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# Factors Responsible for the Carcinoid Spectrum

## A Review

RONALD M. COHEN, B.S., *San Francisco*

● *Current knowledge strongly supports the theory that the carcinoid spectrum reflects the clinical signs of production, by a carcinoid tumor or by metastatic lesions, of one or more humoral substances. Serotonin, the kinins, histamine (and perhaps other amines), adrenocorticotrophic hormone and additional hormones are manufactured by these tumors. Elevated concentrations of serotonin, the kinins and histamine have been found in patients with the carcinoid syndrome, which includes right-sided valvular heart disease, peripheral vasomotor disturbances, bronchoconstriction, borborygmi and an unusual type of cyanosis.*

IN 1930 AND 1931 a patient was described who had the peculiar association of multiple telangiectasis and flushing of a previously cyanotic area of the cheeks, metastatic abdominal carcinomatosis, pulmonary valvular stenosis and paroxysmal attacks of watery diarrhea.<sup>1,2</sup> After reviewing this and other similar case reports,<sup>3</sup> Thorson et al, in 1954, proposed the existence of a carcinoid syndrome made up of malignant carcinoid tumor of the small intestine with metastasis to the liver, right-

sided valvular heart disease, peripheral vasomotor disturbances, bronchoconstriction and an unusual type of cyanosis.<sup>4</sup>

The cyanosis associated with this syndrome differed from the cyanosis of uncomplicated pulmonary stenosis both in time of onset and in color. In uncomplicated pulmonary stenosis, cyanosis is reddish-blue in color and occurs only after the onset of cardiac decompensation; in the carcinoid syndrome, cyanosis frequently appears well before signs of right-sided heart failure and typically progresses from a flush over the face and neck to well demarcated red patches and finally to cyanotic patches. These patches are in a distribution

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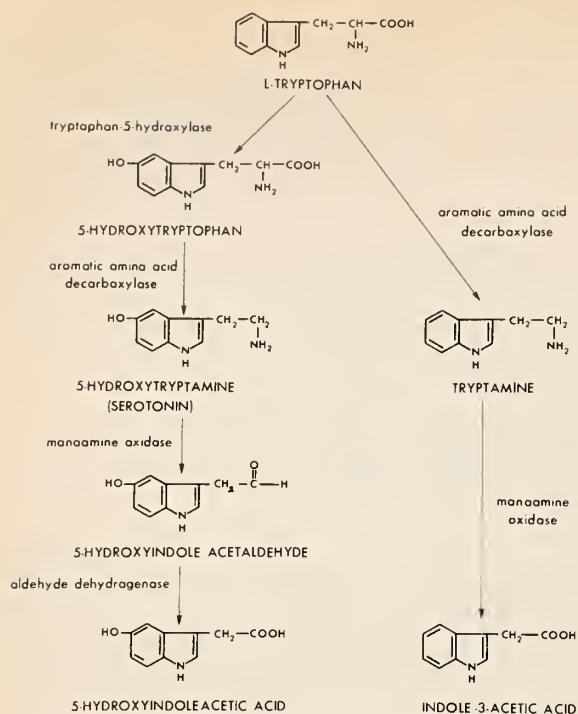


Chart 1.—Major steps in the synthesis and degradation of tryptamine and serotonin (5-hydroxytryptamine).

inconsistent with right-sided valvular heart lesions but could be explained as the product of different states of constriction or dilatation of arterioles, caused, perhaps, by some vasoactive substance from the tumor.

The temporal association of the bronchoconstrictive "asthma attacks" (expiratory stridor and dyspnea) with the later stages of the flush suggested that the same substance caused both phenomena.<sup>5</sup> In addition, although it had been thought that the colic, diarrhea and borborygmi were due to mechanical changes in the bowel caused by the intestinal carcinoid tumor, Thorson and associates believed that a hormonal influence was of greater importance because the borborygmi were almost always associated with the severe cutaneous flushes. Thorson even suggested that the valvular heart lesions might be caused by chronic release of such a substance.<sup>1</sup>

The tumors themselves were unusual in that they grew slowly despite their apparent histological invasiveness. Obvious metastatic lesions were compatible with long life. Jaundice was rare even after tumor metastasis to the liver had largely replaced normal liver tissue. Most patients were reported to die in cardiac failure; few died as a

result of hepatic insufficiency or cachexia.<sup>5</sup> Although metastatic dissemination to the liver and other parenchymatous organs was uncommon in patients with carcinoid tumors, all patients with the carcinoid *syndrome* had extensive hepatic metastasis. Why was the syndrome seen only when these metastatic lesions were present? The possible mechanisms included: (1) decreased ability of the liver to destroy or eliminate a postulated substance, (2) release of the substance from the metastatic lesions adding to the total production, or (3) hepatic injury by the substance, causing a decrease in resistance to growth of hepatic metastatic tumor.

## Serotonin

Thorson and associates investigated the role of serotonin in the carcinoid syndrome. Serotonin, at that time called enteramine, is found in enterochromaffin tissue of the gastrointestinal system (the origin of carcinoid tumors) and is an indole derivative, 5-hydroxytryptamine (Chart 1). Previous investigators had shown that, in experimental animals, serotonin causes pulmonary hypertension and produces apnea, bronchoconstriction,<sup>6,7</sup> and increased intestinal peristalsis after intravenous injection.<sup>8</sup> In addition, it had been found in high concentration in a carcinoid tumor.<sup>9</sup>

Normally, catabolism of serotonin is rapid, but increased concentrations could result if the oxidation of serotonin occurred in the liver and if, once the tumor had embedded in the liver, this process was decreased by hepatic insufficiency. Perhaps the release of large amounts of serotonin was responsible for the manifestations of the carcinoid syndrome. The pharmacologic properties of serotonin could explain the right-sided valvular lesions because serotonin from blood platelets, identical to serotonin from carcinoid tumors, is catabolized to 5-hydroxyindoleacetic acid (5-HIAA) by pulmonary monoamine oxidase as the amine passes through the pulmonary circulation.<sup>10</sup> Any direct effect of serotonin on the heart would be greatest on the structures on the right side in the absence of a shunt from right to left.

On the basis of these observations, Waldenström and Ljungberg measured serotonin concentrations in the serum of carcinoid patients and found them to be elevated, as were the urinary concentrations of one its breakdown products,

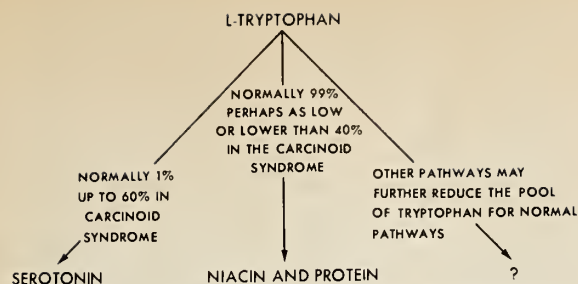


Chart 2.—Postulated alteration in metabolism of tryptophan in patients with the carcinoid syndrome.

5-HIAA.<sup>11</sup> Erspamer's earlier evidence that serotonin stimulated gastrointestinal smooth muscle<sup>12</sup> was a basis for the work of Cole and Bertino,<sup>13</sup> who demonstrated that diarrhea was ameliorated by treatment with chlorpromazine, which had been shown to have an antiserotonin effect.<sup>14</sup> Meldon et al later confirmed this result by controlling diarrhea and malabsorption in certain patients with the serotonin antagonist, methysergide.<sup>15</sup> Reid and Rand had shown that serotonin caused pulmonary vasoconstriction, right ventricular hypertension and bronchoconstriction.<sup>6</sup> Roddie et al simulated the flush in the human forearm by injection of large doses of serotonin into the brachial artery.<sup>16</sup> One interesting case report provided convincing evidence that some vasoactive substance (not exclusive of serotonin) or group of substances was released from carcinoid tumors: Compression of a nodular metastatic lesion in this patient evoked flushing identical to his spontaneous attacks.<sup>17</sup>

However, serotonin antagonists did not control the cutaneous manifestations of the carcinoid syndrome. Moreover, patients in whom the concentration of serotonin in serum was raised artificially did not show symptoms of the carcinoid syndrome; in addition, one patient who had a carcinoid tumor and pronounced elevation of urinary 5-HIAA did not have the syndrome.<sup>18</sup> Although the right-sided valvular lesions had been attributed to pulmonary inactivation of serotonin,<sup>19</sup> Sjoerdsma et al were unable to show significant differences in concentrations of platelet-bound serotonin from peripheral venous blood, pulmonary arteries or brachial arteries of carcinoid patients.<sup>20</sup> Use of platelet-bound serotonin as a measure of whole-blood serotonin was verified when later studies showed that platelets take up almost all available serotonin in the blood.<sup>21</sup>

Sjoerdsma and Udenfriend also investigated the

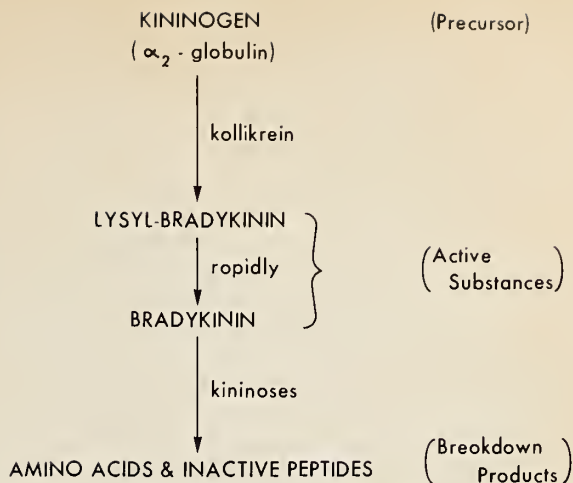


Chart 3.—The kinin peptide system.

effects of alteration of the metabolism of tryptophan (Chart 2), the precursor of serotonin.<sup>22</sup> Although normal persons use only 1 percent of dietary tryptophan for production of serotonin, carcinoid patients direct as much as 60 percent into this pathway, which may leave a deficient amount for production of protein and niacin. Since symptoms of pellagra and hypoalbuminemia may develop in carcinoid patients,<sup>22,23</sup> Sjoerdsma believed that the excess serotonin might be only secondarily responsible for symptoms, deficiency states being more important. However, as discussed later, this idea does not appear likely.

Gottlieb et al transplanted mast-cell tumors in rats; urinary 5-HIAA was increased but lesions comparable to the subendocardial fibrosis seen in patients with the carcinoid syndrome were not produced.<sup>24</sup> Robertson et al showed that intravenous infusions of serotonin did not produce typical flushes, that concentrations of free-plasma serotonin did not correlate well with attacks of flushing and that patients who showed clinical improvement when treated with decarboxylase inhibitors did not always show decreases in serotonin synthesis<sup>25</sup> (see Chart 1). Since emotional stimuli and other stimuli of the autonomic nervous system provoke flushing, Robertson examined the effects of intravenous epinephrine and norepinephrine. A wide range of doses (including those considered subpharmacologic) of catecholamines or amine-releasing agents induced flushing in carcinoid patients. Although concentrations of plasma serotonin were elevated in some patients after injection of catecholamines, there was no similar effect in other patients. Moreover, one patient



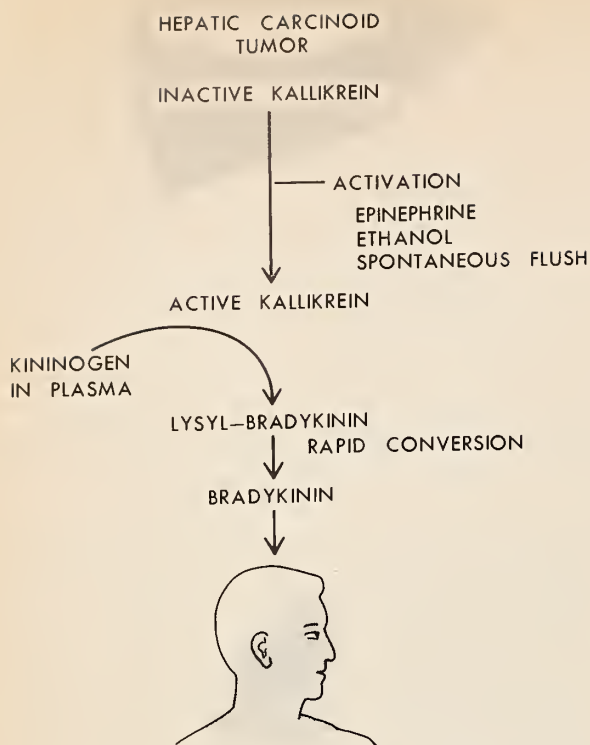


Chart 4.—Postulated mechanisms by which kallikrein and kinins may contribute to the carcinoid flush. The flush mechanism is complex; in some patients, kinin concentrations are normal. (Reprinted by permission from Melmon KL: Kinins in medicine—present and future. *Physiol Pharmacol Physicians* 1:3, June 1966.)

who had a metastatic bronchial carcinoid tumor had normal serotonin concentrations throughout several days of severe flushing. Since the catecholamines were acting indirectly (through release of tumor substances), some other humoral substance was probably at least partially responsible for the symptoms of the carcinoid syndrome.

## The Kinin System

This evidence led Oates et al to study the role of the kinin system in the various symptoms.<sup>26</sup> Kinin peptides are formed by action of kallikrein enzymes on a plasma protein substrate, kininogen (Chart 3). Infusion of one of the peptides, bradykinin, into carcinoid patients resulted in flushes resembling both spontaneous flushes and those produced by catecholamine infusion; in addition, those patients whose spontaneous flushes were associated with hypotension, bradycardia and hyperpnea had these symptoms mimicked. The onset of flushes was more rapid after bradykinin

infusion than after catecholamine infusion, implying that the flushes produced by catecholamines were the result of release of bradykinin by the catecholamines.

To determine whether epinephrine was releasing kinin or was activating tumor kallikrein, concentrations of kinin in hepatic tumor venous blood were measured before and after epinephrine injections in both normal subjects and patients with carcinoid tumors who had metastasis to the liver. Normal subjects showed negligible amounts of kinin before and after administration of epinephrine. Most carcinoid patients showed normal pre-infusion concentrations of kinins, but all carcinoid patients had abnormal elevations of kinin after the infusion. Chymotrypsin denaturation studies demonstrated that the active substance in the hepatic venous samples was similar to synthetic bradykinin.<sup>26</sup> Only negligible amounts of serotonin were found in these samples.

Oates and associates then compared the kallikrein activity in normal livers with that in the hepatic metastatic lesions of carcinoid patients. Kallikrein activity was absent in normal livers, but it ranged from low to extremely high where lesions were present. The lowest level of activity was found in the tumor from a patient without flushes. Other studies showed that epinephrine released this tumor enzyme.

Melmon et al<sup>27</sup> found later that the major peptide formed *in vitro* by extracts of tumor kallikrein was lysyl-bradykinin. Therefore, it seemed that stimuli that provoke flushing (such as epinephrine) act on the carcinoid metastatic lesions to cause release of kallikrein. The kallikrein acts on plasma kininogen to form lysyl-bradykinin which is then rapidly converted to bradykinin. Both peptides can produce the cardiovascular changes associated with hypotensive flushes (Chart 4).

This evidence suggested that the kinins may be mediators of the cutaneous phenomena in some patients regardless of their ability to make serotonin. However, other patients did not have appreciable increases of bradykinin in hepatic venous blood during flushes.<sup>28</sup> Serotonin, alone or in combination with other substances, must have been acting in these patients. In those who showed elevation of both serotonin and bradykinin, the combined effect could produce the net effect.

The kinins are bronchoconstrictors, can decrease peripheral resistance and could mediate



asthma-like attacks. These peptides also can alter capillary permeability and promote an inflammatory process and, thus, could encourage the formation of superficial endocardial heart lesions. Moreover, in contrast to serotonin, the concentration of kinins greatly decreases during transit of the blood from hepatic vein to peripheral artery, an observation compatible with the predominantly right-sided heart lesions seen in this syndrome.

## Other Substances

Serotonin and the kinins are not the only biologically active chemicals which can be manufactured by these tumors. Recent evidence suggests that prostaglandin is another substance formed by the tumor which has the ability to stimulate flushes.<sup>29</sup> Histamine and catecholamines can be made by some tumors, and adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone and other compounds of biological importance may be formed as well.

The variations of the classic carcinoid syndrome may reflect the complex interactions of a number of chemicals produced by the tumor. Bronchial carcinoid tumors, for example, have been associated with excess serotonin production without symptoms, and with secretion of 5-hydroxytryptophan that produces symptoms of central nervous system origin. Patients with bronchial carcinoid tumors apparently are more susceptible to other endocrine disorders (Cushing's disease and acromegaly), suggesting that these carcinoid tumors may be producing ACTH or growth hormone or causing loss of ordinary control mechanisms. Predominately *left*-sided heart lesions and metastasis to bone are also distinctive features of the carcinoid syndrome associated with a bronchial tumor. Thus, a distinctive biochemical potential has been suggested for the bronchial carcinoid tumor. Melmon et al<sup>30</sup> described in patients with bronchial carcinoid tumor a distinctive flushing attack which was more prolonged and severe than that seen with the more common forms of carcinoid tumors. Although serotonin is not the exclusive mediator of common flushes, it is likely that the amine can modify the effects of other vasoactive substances and that it is responsible for some flushes. This is supported by the associated elevation of urinary 5-HIAA and rise in free serotonin in hepatic venous specimens taken during flushing in one patient with a bronchial carcinoid tumor.

A second variation of the carcinoid syndrome was seen in a patient who had a primary carcinoid tumor in the gastric wall and metastatic lesions both in liver and skeleton.<sup>31</sup> Her flushes resembled those produced by injection of histamine, and she was found to excrete large amounts of histamine and its metabolites.

With these variations in mind, Sjoerdsma and Melmon<sup>32</sup> proposed the concept of a carcinoid *spectrum* involving multipotent endocrine tumors capable of producing, at the least, serotonin, kallikrein and histamine and, probably, numerous other substances as well. It is reasonable to assume that the action of one or a combination of substances may cause any of the manifestations of the syndrome. The variations in the characteristics of flushing could be expected to correlate with the substance or substances released from the specific tumor. It has been said that the carcinoid syndrome is the "momentary algebraic sum of these biologically active substances."<sup>33</sup>

## Areas of Future Investigation

Certain inconsistencies in present data suggest important future areas of investigation. For example, deficiency syndromes described in patients with the carcinoid syndrome have been attributed to excessive shunting of tryptophan from normal pathways to production of serotonin (see Chart 2). Niacin deficiency may result and protein synthesis could be altered. However, the greatest tryptophan shunting postulated has been approximately 60 percent. Can a clinical deficiency of niacin result when 40 percent of the tryptophan pool remains for its synthesis? Perhaps some additional tryptophan is directed to *other* pathways of metabolism. That is, overproduction of serotonin may not be the only disturbance in indole metabolism that occurs in the carcinoid syndrome. Perhaps tryptamine (see Chart 1), a decarboxylated derivative of tryptophan, is elevated in the blood of carcinoid patients. Also, 5-hydroxytryptophan is found in some patients with gastric carcinoid tumor because the tumors often lack the decarboxylase enzyme, but the contribution of 5-hydroxytryptophan to the syndrome remains largely uninvestigated. Certainly, top priority must be given to investigation of these and other indole compounds, some of which may be important as mediators of the symptoms of the carcinoid syndrome.

Experimental models that have been used in

the past for investigation of serotonin and the kinins (infusion studies, measurements of concentrations in blood during flushings or other symptomatic episodes) should be used for investigations with substances such as tryptamine, 5-hydroxytryptophan and other indoles.

Further biochemical and pharmacologic study of imidazoles is also indicated. The determination of concentrations of plasma histamine during flushes, especially in patients with gastric carcinoid syndrome, would be worthwhile.

Hasty conclusions from such studies must be avoided, however, since substances found in the tumor and blood may not be primarily responsible for symptoms. Many substances can release other active substances. Thus, even if a substance is found in high concentration in the tumor or circulation, the precise pathogenic role it plays may be elusive.

Research on the many aspects of the carcinoid syndrome has benefited the fields of gastroenterology, physiology and pharmacology. Observation of the behavior of malignant argentaffine cells has provided the gastroenterologist with insight into the role of normal argentaffine cells. The physiologist now has a model for studying the effects of serotonin and the kinin system. The pharmacologist, in his search for therapeutic agents, has helped to shed light on many of the questions that still remain in the study of the carcinoid spectrum.

Earlier workers had been convinced of the importance of serotonin alone, as expressed in the following limerick by Bean:

This man was addicted to moanin'  
Confusion, edema and groanin',  
Intestinal rushes,  
Great tri-colored blushes,  
And died of too much serotonin.<sup>31</sup>

In view of our present knowledge of the complexity of this biological system, this seems an oversimplification. Accordingly, later workers have avoided such all-encompassing statements. For the present, the carcinoid spectrum must be viewed as an interaction of substances leading to the net effect seen in each patient. There remains a good deal of work to be done before an understanding of this endocrinologic maze can be reached.

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# The Proctologic Examination—A Guide

JAMES H. MACLEOD, M.D., *Los Angeles*

BESIDES BEING THE SITE of many other afflictions, the distal colon and rectum is the area in which 65 to 75 percent of colorectal cancers and 10 percent of all fatal cancers occur.<sup>1,2</sup> Colorectal cancer has been termed the most important single type of cancer by the American Cancer Society, which has stated: "Sigmoidoscopy can lead to the saving of more lives than any other step in the annual checkup."<sup>1</sup>

The anorectal examination all too often consists of a cursory waggling of the finger in the rectal ampulla, whereas it should be carried out in a systematic fashion. Sigmoidoscopy is frequently regarded as a specialized procedure which is difficult, expensive and time-consuming, though in fact, it is none of these.

After a history of symptoms has been elicited, a systematic examination should be carried out according to a definite plan:

1. Perianal examination
2. Digital examination
3. Anoscopic examination
4. Sigmoidoscopic examination

The equipment required is listed in Table 1.

## Perianal Examination

### *Inspection*

The buttocks, sacrococcygeal area and perineum are examined as well as the perianum. The presence or absence of the features listed in Table 2 are noted.

This part of the examination is not complete until the buttocks and the edges of the anal orifice have been retracted firmly so that not only the anal verge but the greater part of the anal

canal can be seen, often to the dentate line. For example, if an anal fissure is present, at least its lower portion can be seen by means of this maneuver, without the aid of any instruments.

### *Palpation*

The perianum is palpated for areas of tenderness, induration or heat if an abscess is suspected.

Scars are palpated and their induration or pliability noted.

A fistula tract may be palpated as a cord-like structure when traction is placed on it, and pressure may result in the release of a bead of pus from its external opening.

Bi-digital examination may reveal a small lesion such as a perianal abscess which is otherwise not apparent. It is performed in a clockwise fashion, palpating the tissues between the examining finger in the anal canal and the externally placed thumb of the same hand, the suspicious area being compared with adjacent tissues and with the corresponding tissues on the other side.

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TABLE 1.—*Equipment Needed for Proctologic Examination*

---

#### *Standard*

1. Table (the ordinary examining table is satisfactory if the lateral position is used).
2. Examining light.
3. Finger cots or gloves.
4. Anoscope—tubular or slotted.
5. Long, cotton-tipped applicators.
6. Sigmoidoscope—conventional or fiberoptic. Disposable anoscopes and sigmoidoscopes are available.

*Optional* (use of this equipment requires that a toilet be readily accessible)

1. Suction apparatus (a simple and inexpensive apparatus which can be attached to a tap is satisfactory).
2. Disposable enema equipment.

Submitted April 15, 1970.

Reprint requests to: 640 South Van Vicente Boulevard, Los Angeles, Ca. 90048 (Dr. J. H. MacLeod).

**TABLE 2.—Features to be Noted on Examination of the Perianum**

- Soiling—due to incontinence, fecal impaction or lack of fastidiousness.
- Discharge or seepage.
- Dermatitis or evidence of pruritus, such as excoriations.
- External invaders—lice, worms.
- The multiple wart-like growths of condylomata acuminata. (Condylomata lata, due to syphilis, differ in appearance and are far less common.)
- Skin tags, including a “sentinel pile” below an anal fissure.
- The bulge of external hemorrhoids.
- The tense swelling of a perianal hematoma (“thrombosed hemorrhoid” is a misnomer).
- The bulging and redness of an abscess of the perianum or ischiorectal space.
- The multiple superficial abscesses and sinuses of hidradenitis suppurativa.
- The external opening of an anal fistula.
- Exposed mucosa (may be due to prolapsing hemorrhoids, to mucosal prolapse, or to eversion caused by previous operation).
- Scars of previous operation.
- Squamous carcinoma, which may occur on the perianum or in the anal canal. Any suspicious or bizarre lesion should be biopsied (it should be remembered that the lymphatic drainage from the perianum and anal canal is to the inguinal nodes).
- Dermatologic lesions. Any tumor or other disease of the skin may also affect this area.

## Digital Examination

Advising the patient as to what to expect before each step in the examination helps to obtain maximum relaxation and cooperation. Gentleness is vitally important for the same reason.

The finger cot or glove should be well lubricated. The finger is inserted with the greater dimension, that is its breadth, parallel to the antere-posterior axis, since the latter is the greater diameter of the anal canal. This is especially important if there is a painful anal lesion. Steady, gentle pressure applied in the axis of the anal canal, in the direction of the umbilicus, will relax the sphincter.

## Anal Canal

The following should be noted:

- Sphincter tone—degree of laxity, spasm or stenosis
- Tenderness or irregularity—due to anal fissure or ulcer
- Internal opening of a fistula

- Scar of previous surgical procedure
- Hypertrophied papilla
- Carcinoma

Internal hemorrhoids are not usually palpable, since they consist only of collapsible veins and overlying mucous membrane—unless they have been recently injected or thrombosis has occurred. Occasionally they are palpable as fibrous cords if there has been longstanding chronic inflammation.

## Rectum

The length of the average finger from the digital web is 3 inches. With pressure the effective length may be 4 inches; and, with the patient bearing down, lesions even higher may be palpated, well above the peritoneal reflection. The level reached will vary also with the patient's build and degree of relaxation. A working classification of palpable lesions and structures is shown in Table 3.

## Miscellaneous Points

- The coccyx can best be examined by a bi-digital or bi-manual examination between the finger in the rectal ampulla and the externally placed thumb or hand.
- Levator muscle tenderness may account for vague rectal pain.
- In females the condition of the posterior vaginal wall should be noted and the presence or absence of a rectocele should be confirmed by digital rectal examination.
- In the presence of endometriosis, the rectovaginal septum is frequently involved. This is best detected by a bi-digital (rectovaginal) examination.
- When an intraperitoneal mass is suspected, a bi-manual recto-abdominal examination may be helpful.
- The fingertip should be examined on withdrawal and the presence or absence of blood, mucus or pus noted, as well as the color and character of the feces. Fecal specimens may also be tested for occult blood.

## Anoscopic Examination

Besides examination by retraction of the buttocks and perianum, the anal canal can often be examined during withdrawal of the sigmoidoscope. A more detailed examination can be car-



ried out with either the tubular or slotted anoscope and the following conditions detected:

- Internal hemorrhoids
- Internal opening of a fistula—a bead of pus may be expressed into the anal canal by pressure on the perianum
- Anal fissure or ulcer
- Intra-anal condylomata
- Carcinoma, either squamous carcinoma of the anal canal or adenocarcinoma extending distally from the rectum

## Sigmoidoscopic Examination

Besides its importance in the diagnosis of cancer, sigmoidoscopic examination is useful in diagnosing other rectal tumors, such as simple and

**TABLE 3.—Classification of Palpable Lesions and Normally Palpable Structures (Modified from Nesselrod<sup>2</sup>)**

### *Intrinsic*

- Intraluminal
  - Impaction.
  - Foreign bodies.
- Mucosal and Submucosal
  - Inflammatory
    - Recently thrombosed or injected hemorrhoids.
    - Submucosal abscesses.
    - Large discrete ulcers.
    - Strictures.
  - Traumatic
    - Enema tip injuries.
    - Impalement injuries.
  - Neoplastic
    - Polyps.
    - Carcinoid tissue.
    - Carcinoma.
- Intramural
  - Endometrial deposits.
  - Tumors, benign or malignant.

### *Extrinsic (extramural, extrarectal)*

<i>Anterior</i>		<i>Normal</i>	<i>Abnormal</i>
	Prostate or cervix.		Pelvic masses:
	Peritoneum (female especially).		Neoplastic—Carcinoma of sigmoid, of small bowel, of ovary.
	Ovary in cul-de-sac.		Inflammatory—Inflamed appendix; regional ileitis; sigmoid diverticulitis.
<i>Lateral</i>			
	Ischial tuberosity.		Pelvic masses (as above).
	Ischial spine.		
<i>Posterior</i>			
	Coccyx.		Retrorectal abscesses.
	Sacrum.		Presacral tumors—e.g. teratoma, chordoma.
			Bone tumors.

villous adenomas, as well as ulcerative colitis or proctitis and other less common conditions.

## Preparation

In most cases a complete examination, including sigmoidoscopy, can be done with no preparation of the patient whatsoever, and it is preferable that this be done.

A laxative is unreliable, may render examination more difficult rather than less so, and may alter the appearance of the mucosa. Enemas also tend to irritate the mucosa and may obscure early proctitis or colitis. More important, the enema may wash away blood in the rectal lumen which comes from a lesion above the range of the sigmoidoscopy, so that a valuable clue is lost. If an enema is necessary, before it is given the presence or absence of blood in the lumen should be determined with the sigmoidoscopy.

If the optional, as well as the essential equipment described in Table 1 is available, almost all patients can be sigmoidoscopically examined in the office. Without such equipment those who require cleansing will have to return after cleansing or the sigmoidoscopic examination done elsewhere.

## Positioning

A few moments given to proper positioning will make the examination much easier.

If the lateral position is used, the patient is placed obliquely on the table, on his left side, with the buttocks well over the edge so that there is room to manipulate the instrument in all planes. The hips are flexed fully and the knees to 90 degrees. The uppermost shoulder is allowed to fall forward and the patient is asked to relax as much as possible while breathing gently with his mouth open. He is advised of all possible sensations before they occur, such as a feeling of rectal fullness, of urgency and of abdominal cramps.

Many examiners prefer the knee-chest position, since it is said to render passage of the sigmoidoscopy easier by straightening out the sigmoid loop. Doubt has been cast on this supposition recently<sup>4</sup> and the increased tension produced usually offsets the questionable advantages of this position. The lateral position is more comfortable for the patient and, moreover, does not require a special table.



## Procedure

A reasonable degree of proficiency can and should be acquired to minimize both the risk of injury and unnecessary discomfort to the patient.

A warm sigmoidoscope, well lubricated and with the obturator in place, is inserted through the anal canal, in the direction of the umbilicus, by steady pressure. The resistance of the anal sphincter is felt to diminish as the rectal ampulla is entered. This is the only blind part of the procedure and should be preceded by a digital examination in order to dilate the sphincter and, more important, rule out the presence of any lesion in the rectal ampulla which might be aggravated by the tip of the sigmoidoscope.

The next step is to remove the obturator with one hand while holding the sigmoidoscope firmly with the other, and the tip of the instrument then is swung 90 degrees posteriorly in the rectal ampulla and is passed gently through the mid-rectum, with manipulation as necessary to move it through the mucosal folds and valves as necessary. Air is gently insufflated occasionally as required and it may cause a sensation of rectal fullness. Cotton-tipped applicators are used as necessary.

Passage of the instrument to the rectosigmoid junction, 12 to 15 centimeters from the anal verge, is easy in most patients. At about this point, the smooth rectal mucosa gives way to the concentric rugae of the distal sigmoid colon. Here too, the bowel passes anteriorly over the sacral promontory and may then turn in any direction as the tip is pushed proximally. For this reason, there is no prescribed method of manipulation at this point. The instrument is turned and pressed so that the lumen is seen and followed at all times, until the sigmoidoscope has been passed to its full length. At this point gentle air insufflation will often open the lumen and permit inspection of it for several centimeters proximal to the tip of the sigmoidoscope.

Passage beyond the rectosigmoid junction is sometimes difficult for various reasons:

- The mesosigmoid becomes shorter in this region, lessening the mobility of the bowel.
- Circular muscle spasm may be caused by roughness in technique, excessive air insufflation or the patient's inability to relax. The spasm will usually abate after a wait of a minute or so. If it does not, the examination should be discon-

tinued. Above all, the instrument should not be forced past this area.

- There may be fixation of the bowel due to adhesions caused by previous or current inflammation, such as diverticulitis, or by a previous operation.

In such cases, it is better to discontinue the examination than to attempt to force the instrument beyond and run the risk of perforation of the bowel. Once a reasonable degree of proficiency has been attained, sigmoidoscopic examination can be extended to 25 cm in 85 to 90 percent of patients; and viewing to only 15 cm is worthwhile, since 50 to 55 percent of colorectal carcinomas can be detected<sup>1</sup>—and perhaps more, since the distance measured by the sigmoidoscope may be less than that actually reached.<sup>5</sup> If there is reason to suspect a lesion above this point, barium enema examination may be performed, since it is quite reliable above the level of 15 cm from the anal verge.

While the sigmoidoscope is being passed, main attention is given to the manipulative technique of advancing it through the lumen, and only a partial examination is carried out. Detailed examination therefore must be carried out during withdrawal of the instrument. So that every portion of the mucosa can be inspected, the instrument is rotated in a tight spiral as it is withdrawn. Particular attention should be paid to the upper surfaces of the rectal valves, since these may harbor small lesions which are easily missed unless the valve is depressed with the tip of the instrument. Lesions in the posterior rectal ampulla also may be missed, since the posterior wall of the ampulla lies at a 90 degree angle to the anal canal; if such a lesion is villous in nature, it may be so soft as to have been missed on digital examination.

One should learn the appearance of the normal rectal mucosa—the color and vascular pattern with the submucosal vessels showing as a fine network. These characteristics may be altered or obscured in the presence of disease. If any doubt exists as to whether the mucosa is normal, the “touch test” may be employed: The mucosa is touched gently but firmly with a cotton-tipped applicator, and blood stains on the applicator indicate abnormality.

The entire proctologic examination, including sigmoidoscopy, should not take more than 5 min-

utes. Further time is usually unrewarding and most trying to the patient.

The procedure can be performed safely and with very little discomfort to the patient if the following rules are observed:

- Introduction of the sigmoidoscope must always be preceded by a digital examination (for reasons already given).

- The sigmoidoscope must never be advanced unless the lumen ahead can be seen. If the lumen is not visualized, the instrument is probably in a mucosal pocket and should be withdrawn several centimeters until the lumen is visible. Proximal passage is then begun again.

- The sigmoidoscope must never be forced. This is particularly true in cases of suspected ulcerative colitis, as the bowel wall may be very friable.

- If the sigmoidoscope cannot be passed to its full length within a few minutes, the examination should be discontinued.

If these rules are observed, perforation of the bowel, which is the chief danger in sigmoidoscopic examination, will rarely occur. In addition, the patient is more likely to be willing to return for further examination.

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#### THE SCREENING QUESTIONS IN NEUROLOGIC DISORDERS

"In taking the history of patients with a suspected neurologic disorder, ten items seem to be of particular importance. Though there is some overlap, most of these items are not covered during the regular physical examination. They include: (1) a history of headache or pain (it is important in this regard to include the quality, intensity, and location of the pain and also whether associated with nausea, vomiting or both); (2) changes in concentration and memory; (3) periods of partial or complete loss of awareness (these losses can be associated with delusions or hallucinations); (4) convulsions or abnormal movements affecting the body or parts of the body; (5) weakness or stiffness; (6) changes in gait, posture, or facial expression; (7) loss of sensation, or paresthesias or pain . . . ; (8) changes in vision, including spots before the eyes and diplopia; (9) loss of hearing or vertigo and (10) difficulty in swallowing or voice change, such as hoarseness. These items will screen most of the historical problems of importance in neurologic diagnosis."

—ELI S. GOLDENSOHN, M.D., New York City  
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## Sexual Differentiation: The Development Of Maleness and Femaleness

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ALL OF THE AVAILABLE EVIDENCE leads to the conclusion that in development the process of becoming a male involves a number of complicated steps which are unnecessary in order for femaleness to occur. Thus it appears that the basic primordial sexual differentiation of most mammalian species is female, and maleness is dependent upon a number of essential additive steps in the developmental process in order to produce those changes in reproductive physiology and behavior that characterize the male.

There are at least four major events which are needed in order for the developing embryo to become male. If any of these is altered significantly the tendency of the embryo is to continue in its development as a female or a genetic male with many female characteristics. Initially, in order for maleness to occur at all there must be present in the genes an X and a Y chromosome. The development of the female involves a double X chromosome. In humans 46 chromosomes are normally found; the major difference chromosomally between the male and the female is the presence of a Y chromosome in the male and the absence of a Y chromosome in the female. In humans who have been found to have 45 chromosomes it is due to the fact that they have only one X chromosome and lack a Y chromosome. Such XO persons are

female. Other individuals have been found to have 47 chromosomes because they have two X chromosomes and a Y chromosome. Such XXY persons are males. The Y chromosome then determines maleness, normally in XY individuals, abnormally in XXY individuals. The absence of the Y chromosome determines females, normally in XX individuals, abnormally in XO individuals. This, then, is the first example of what we are calling an additive process; that is, the addition of a Y chromosome is necessary to initiate the very process of maleness.

The next critical event in becoming a male involves that of the formation of the male gonads, the testes. The mammalian sex organs, initially in development, appear as two genital ridges in the fetus. Each ridge has an inner mass of medullary tissue and an outer cortical mass. This indifferent gonad can go either in the direction of the formation of an ovary or the formation of the testes. If the medulla begins to reorganize itself the cortex atrophies and disappears, or conversely, if the cortex develops and the medulla retrogresses or disappears, then two different organs are formed. If the medulla develops, the resulting organ is a testis; if the cortex develops, then the resulting gonad is an ovary.

Recent information indicates that the formation of the testes precedes that of the formation of the ovaries in development. Although there is little information as to the mechanism whereby

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the indifferent genital ridge becomes either a testis or an ovary, it does appear that some active secretory process is necessary in order to cause the medullary tissue to develop. If this process does not happen, the tendency of the organism's indifferent genital ridge is to develop as an ovary. Once the testes are formed, however, there are still further vital steps that are necessary in order for the organism to become totally male. That is, the fetal testes must secrete a duct-organizing substance and then male hormones (androgens) in order for this embryo to become male. The secretion of a substance from the fetal male testes is absolutely essential for the anatomical differentiation of the male and for the functional differentiation of the male.

During intrauterine life the fetus is equipped with the primordia of both male and female genital ducts. The Müllerian ducts serve as an anlage of the uterus and fallopian tubes; whereas the Wolffian ducts have the potentiality of differentiating further into the epididymis, vas deferens, seminal vesicles and ejaculatory duct of the male. In humans, during the third fetal month, either the Müllerian or Wolffian ducts complete their own development while involution occurs simultaneously in the opposite structures. It has been clearly demonstrated by the eminent embryologist, Alfred Jost,<sup>1</sup> that secretions from the fetal testes play a decisive role in determining the direction of genital duct development. In the presence of functional testes the Müllerian structures involute while the Wolffian ducts complete their development; whereas in the absence of the testes the Wolffian ducts are reabsorbed and the Müllerian structures mature.

Female development is not contingent on the presence of an ovary, since equally good development of the uterus and tubes will take place if no ovary is present. The influence of the fetal testes on duct development is unilateral since early removal of one testis leads to Müllerian development on that side while the male duct normally develops on the side on which the testis remains intact. The systemic injection of androgen to an early embryo fails to duplicate the action of the fetal testes. When androgen is applied locally under conditions of extremely high dosage the Wolffian ducts exhibit signs of stimulation, but no inhibitory effect on Müllerian elements has been

observed. These data have led to the belief that the fetal testes secrete a duct-organizing substance which is distinct from androgen.

However, the presence of the normal male anatomical structure still does not insure that the developing embryo will become functionally male. What do we mean by the concept of functionally male? If we were to examine in detail some of the major differences between male and female sexuality we would note that there are sex dimorphisms in many aspects of reproductive physiology, stress physiology, metabolic processes, and behavior. In particular, with regard to reproductive physiology and the behavioral aspects of maleness and femaleness, it does appear that one of the principal actions of androgen during development is to organize the immature central nervous system into that of the male. Once again we are talking about an active process; that is, the presence of androgen during development acts upon the brain to program, in effect, patterns of maleness.<sup>2,3</sup> The absence of androgen permits the ongoing process of femaleness to pursue its natural course. The evidence to support this theory is now abundant.

Let us begin by examining one of the principal distinctions between males and females with regard to reproductive physiology. In most species of mammals the female has a cyclic pattern of ovulation. The human female ovulates about every 28 days, the guinea pig about every 15, and the rat every 4 to 5 days. In cyclic fashion the anterior pituitary delivers to the ovary follicle-stimulating hormone (FSH) which promotes the growth of the Graafian follicle which produces estrogen and also houses the ova to be released at the times of ovulation. The anterior pituitary also releases luteinizing hormone (LH) which induces the formation of the corpora lutea and triggers ovulation. The formation of corpora lutea is clear evidence that ovulation has occurred. There is a continuing ongoing feedback system which is only interrupted in the normal cycling female by the onset of pregnancy. The male, in contrast, shows no such cyclicality. Its testes continually receive from the pituitary luteinizing hormone, but this luteinizing hormone in the male causes the development of the interstitial cells of the testes, those cells which are predominantly responsible for testosterone production. Thus, the pattern of hormone production from the pituitary, in order



to maintain the process of ovulation in the female, is indeed a cyclic one. The process of production of hormones from the male is for the most part noncyclic.

It has been demonstrated that the pituitary is in itself not sexually differentiated,<sup>4</sup> so that if a female pituitary is transplanted into a male, normal male functions will be maintained. Conversely, if the male pituitary is transplanted into a normal female, complete female function will also be maintained. The implications of these studies are that pituitary regulation comes not from the pituitary itself but from some other controlling mechanism. All of the available evidence indicates that the controlling mechanisms are somewhere in the central nervous system. The clearest demonstration of the role of the testes in modulating central nervous system control of reproduction comes from studies in which newborn rats have been deprived of their testes.

It has been dramatically demonstrated, most recently by Professor Geoffrey Harris<sup>2</sup> that when these neonatally castrated males are allowed to grow, their pattern of pituitary release of those hormones which regulate gonadal function (FSH and LH) is cyclic and indistinguishable from that of a normal female. Thus, if an ovary is transplanted into the adult animal who has been castrated as a newborn, this ovary shows full cyclic ovulation. Thus, we have a case where a genetic male with XY chromosomes, a morphological male showing all of the sexual differentiation of anatomical structures, still is responding, in the central nervous system, as a female. It should be noted that if, following castration, the male is given a single injection of testosterone, the ovulation that is seen in adulthood no longer occurs. Furthermore, if the newborn female is given a single injection of testosterone shortly after birth, she is also acyclic and incapable of maintaining normal patterns of ovulation.<sup>5</sup>

These studies provide one line of evidence which indicates that the maleness is dependent upon having a male central nervous system and that in order to have a male central nervous system the fetal and neonatal testes must secrete androgen which presumably acts upon the brain to differentiate it into that of the male. There are definite critical periods in development for these events to occur; thus, in the rat if the newborn male is castrated within 24 hours after birth the

central nervous system will continue to be female. If, however, this period exceeds approximately 72 hours, then the process is now irreversible and the male central nervous system has been permanently established.

The hypothesis of sexual differentiation of the brain is further substantiated when one closely examines the influence of the presence or absence of testosterone in both the newborn male and female rat on adult sexual behavior. In most mammalian species the hormones emanating from the ovary and the testes have profound control of sexual behavior. In normal circumstances the female rat becomes sexually receptive during a period in the estrous cycle when there exists the appropriate hormonal balance between the ovarian hormones, estrogen and progesterone, that results in ovulation.<sup>6</sup> If the female is deprived of the appropriate circulating hormones by ovariectomy, sexual receptivity is immediately abolished. However, when the appropriate hormones are replaced, either in the form of chronic high doses of estrogen, or small doses of estrogen followed by progesterone, sexual behavior appears within a very short time following progesterone administration. Sexual behavior of the male rat involves a much more complex pattern of mounts with intromissions and ejaculation. In contrast to the cyclic pattern of receptivity exhibited by the female, the male is acyclic in his sexual behavior and will under normal circumstances copulate as long as there is an appropriate stimulus object.

The biological adaptiveness of these two different patterns is readily apparent; thus, for the female of most mammalian species, sexual receptivity is consistent with ovulation, so that almost every sexual contact would result in pregnancy. However, if the male also had a cyclic pattern of sexual activity, then the conditions under which pregnancy would occur would at least be infinitely more complex. Again, in contrast to the female, when the male is castrated there ensues a period of time during which the male is sexually active, even in the absence of circulating hormones. Eventually, however, the male will cease normal sexual activity and, following replacement with testosterone, will resume behavior that is indistinguishable from the normal intact male. However, no amount of estrogen and progesterone has yet proved capable of reliably eliciting, in an adult castrate male, patterns of sexual behavior that are typical of the normal female.



The evidence regarding normal patterns of sexual behavior and their dependence upon circulating hormones is consistent with the hypothesis that there are differences between the male and female brain with regard to patterns of hormone secretion and behavior. Thus, female sexual receptivity is easily elicited with the appropriate regime of estrogen and progesterone replacements following removal of the ovary. In the male these behaviors appear to be completely suppressed and cannot be elicited with doses of estrogen and progesterone that are a thousand-fold higher than those required in the female. Therefore, one of the primary aspects of sexual differentiation in the rat appears to be the suppression of the capacity in the normal male to respond to estrogen and progesterone.

Although there is a firm underlying assumption that behavior reflects in some ways the action of the central nervous system, there is clear evidence that sex hormones can act directly on the brain. Implants of synthetic estrogen (stilbestrol) in one area of the brain, the hypothalamus, of female cats evoke female sexual behavior, although the cats do not show the usual physiological signs of estrus.<sup>7</sup> In similar experiments implants of testosterone in the brains of castrated male rats also elicited male sexual behavior, although again there was no sign of the effect of this testosterone on the anatomical structures of the male reproductive system.<sup>8</sup>

The influence of androgen during development on sexual behavior patterns is demonstrated by the now two classic approaches to the problem: one is the administration of testosterone to an organism which normally would not have testosterone—that is, the female—and the other is the removal of the testosterone-producing organs, the testes, during a critical period in the development of the male. In the case of the female, a single injection of an appropriate dose of testosterone<sup>9</sup> is capable of abolishing female patterns of sexual receptivity. This female not only fails to show any signs of sexual receptivity under normal circumstances but also when the ovary is removed sexual behavior cannot be elicited by the appropriate replacement of estrogen and progesterone which normally would elicit complete sexual receptivity in non-testosterone treated females with ovaries removed. Further, these females treated neonatally with testosterone will show some increase in male patterns of sexual behavior follow-

ing injections of androgen in adulthood.<sup>5</sup> Conversely, although it is extremely difficult, if not impossible, to elicit female receptivity in a male that has been castrated as an adult, when the testes are removed within 24 hours after birth sexual responses elicited by estrogen and progesterone in adulthood are completely indistinguishable from those of a normal female.<sup>10</sup> Not only are they indistinguishable to the human observer but normal adult males will respond to these estrogen and progesterone treated neonatal castrated males as if they were females in heat. Once again, a single injection of testosterone given shortly after castration to the newborn animal will completely reverse all of these effects.

We have thus far assumed that the function of gonadal hormones in infancy is to organize the central nervous system with regard to neuroendocrine control of behavior. Although we have focused primarily on reproductive behavior, numerous reports in the literature have indicated that there are sex differences in nonsexual behavior. If indeed we are to make a convincing argument that the effects of androgen are to influence the central nervous system, then it seems reasonable to assume that other patterns of sex differences would also be influenced by these same hormones. There are now well-reported differences<sup>2</sup> in activity patterns between males and females. Activity patterns of the female closely parallel estrous cycle activity and during the estrous phase of the cycle females show high peaks of activity. In contrast, the male shows no apparent activity cycle and over-all activity levels are much lower. These female activity cycles can be mimicked in the neonatal castrated male by an ovarian transplant in adulthood. Thus, before the transplantation of the ovary the male which has been castrated as a newborn, shows a low level of random activity. However, the appearance of the corpora lutea in the transplanted ovary marks the onset of female activity cycles which are again indistinguishable from those of normal females. During this period the neonatally castrated rat with the transplanted ovary also becomes sexually receptive in cycles. Sex dimorphisms have also been noted in other patterns of behavior, including emotional responses to novel situations, and aggressive behavior.

Recently we have investigated<sup>11</sup> the effects of androgen on experimentally induced aggressive

behavior. Males and females differ markedly in the amount of aggressive behavior elicited by exposure to electric shock, with males fighting significantly more than females. Further, if males are castrated at weaning, their aggressive behavior is reduced but not quite to the level seen in normal females. However, when they receive replacement treatment with testosterone these males show significant increases in aggressive behavior equivalent to that observed in the normal intact male. The female, however, shows no increase in aggressive behavior following testosterone treatment. In male rats castrated as newborns, aggressive behavior is suppressed and supramaximal doses of androgen given to the adult organism do not increase aggressive behavior as seen in castrated weanling rats. Thus again we have an example of the maintenance of feminine patterns of behavior when the newborn male is castrated. Further, there appears in this experiment that property of the central nervous system which has been observed throughout many of the experiments discussed thus far, namely that the female brain is differentially responsive to androgen and that many behaviors which are elicited by androgen in the normal males are generally incapable of appearing on androgen stimulation in the normal female or its equivalent, the male that is castrated during the critical period in development.

Examination of developmental patterns of the testes indicates that during the late prenatal periods and in the rat for a brief period of time postnatally, the fetal and neonatal testes exhibit a high degree of endocrine activity. There is active production of testosterone from the testes. However, after this brief period of activity the testes become very quiescent and there is very little androgen production until just before puberty. One can infer that this period of high androgen activity during a critical period in development is essential for the sexual differentiation of the brain.

For obvious reasons, the research we have discussed thus far has been accomplished mainly in laboratory animals. The closest human analogue which demonstrates the influence of testosterone during development on subsequent sexuality is the syndrome of testicular feminization. Clinically, the internal ducts are predominantly male. The external genitalia, however, resemble those

of the female, although the vagina is shallow and ends blindly in a pouch. At adolescence, female secondary sex characteristics develop — notably well-developed breasts and rounding of the body contours. Etiologically this disorder can be attributed to a peculiar process by which the target tissues become androgen resistant. Thus, although the testes produce the appropriate hormones, apparently the tissues remain insensitive to this hormone and consequently produce the syndrome of overt feminization. The clinical literature is abundant with numerous instances of gender role reversals as a consequence of pathological conditions which result in sexual ambiguities, in particular, penis-like structures in female offspring. However, it has been clearly demonstrated by Money and co-workers<sup>12</sup> that to a very large extent the gender role assigned to the individual who is born with distorted external genitalia is dependent on the way in which the individual is reared. Thus if the individual with such sexual ambiguity is treated as a male, it will generally assume a male gender role, although it may indeed have ovaries. Conversely, if the individual is treated during development as a female, it will thus continue female, although again the internal genitalia and chromosomal patterns may be those of a male. Thus, at least as far as the human is concerned, there is an additional process in development which involves the establishment of gender role as a function of learning.

What we have tried to demonstrate in this paper is that for maleness to occur there are several unique active processes which must take place with exquisite timing during development. Perhaps of more importance is the influence that hormones have on the developing central nervous system to organize and establish patterns of physiology and behavior that will determine the organism's life history. All the experimental evidence presented here supports the view that alterations in hormonal status in the newborn animal have profound and permanent effects on the animal's subsequent biological functioning.

Although we have dealt specifically with only the gonadal hormones, there is evidence<sup>13,14</sup> indicating that both changes in thyroid and adrenal function can also permanently affect the developing nervous system. Although we do not as yet have any evidence as to the mechanisms whereby these hormones act upon the central nervous system, we believe that this is indeed one of the more



exciting, newer concepts to emerge from developmental biology and if nothing else, indicates that the developing organism is extremely sensitive to hormones and certainly suggests a judicious use of hormones during those critical periods in the development of the organism which may be most profoundly affected by hormonal changes in the environment.

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#### LID RETRACTION AS A SIGNAL OF CHANGE IN THYROID FUNCTION

"One of the things that often points to changes in thyroid function is upper lid retraction. At least in the patients we have seen, this problem occurs as frequently without exophthalmos as it does with it. It may go unnoticed for a number of years. Often the lid will gradually creep up over a period of time and then stop. The difficulty that comes with it is due to exposure of the lower portion of the cornea when the patient is asleep. These individuals do not completely close their eyes; the cornea rolls down slightly and one gets stippling along the lower portion of the limbus. This stippling often leads to complaints by the patients . . . of a foreign body sensation. It's not very evident by routine slit-lamp examination. Usually you have to stain the cornea in order to see it. If you're going to check for inability to close the lids, ask the patient to close his eyes as if he were sleeping because virtually all of these patients can get their lids against each other if they clamp down real hard. You really want to know what's happening when they're relaxed and the lids are just lying against the globe."

—JAMES E. MILLER, M.D., Albany, N.Y.  
Extracted from *Audio-Digest Ophthalmology*,  
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# Gonococcal Sepsis and Arthritis

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. EDELMAN:\* The topic for discussion today is gonococcal sepsis and arthritis. The case will be presented by Dr. Feldman.

DR. FELDMAN:† The patient, a 26-year-old white man, had been in his usual state of excellent health until three days before admission to hospital when generalized malaise, diffuse joint stiffness, and tenderness around the third right proximal interphalangeal joint developed. He noted prominent pain on motion of the knees, but said that these joints were neither red nor swollen. At the same time he felt feverish and had several shaking chills. The next day pustules appeared on the dorsum of his left hand, on the thigh, and later on the palmar aspects of the fingers and on the soles of his feet. The skin lesions began as small, red, tender spots which progressed to central pustule formation. He punctured one lesion, and purulent material exuded.

The patient had had numerous sexual contacts, the most recent one ten days before admission. He denied urinary symptoms or penile discharge, but an open sore near the penile corona had been healing poorly. There was no history of venereal disease. Although he denied regular use of drugs, he had given himself an intravenous injection of amphetamine ten days before admission.

On physical examination, the patient was alert and afebrile and the vital signs were within normal limits. Pertinent physical findings were confined to the skin, joints and genitalia. There were

several tender red macules 5 to 10 mm in diameter with raised central pustules or necrotic centers on both hands, the left thigh and the left great toe. Periarticular tenderness was present around the third right proximal interphalangeal joint, but no other abnormalities were apparent. A partially healed ulcerative lesion was present near the penile corona, which was erythematous and tender. Purulent material could be expressed from the urethra. No cardiac murmurs or other stigmata of endocarditis were present. The abdomen was soft and there was no organomegaly or hepatic friction rub.

Leukocytes in peripheral blood numbered 7500 cells per cu mm with a normal differential count. The hemoglobin was 14 gm per 100 ml. Urinalysis was within normal limits. Gram stains of smears prepared from the skin pustules revealed numerous polymorphonuclear leukocytes; no microorganisms were seen. Similar smears of the urethral exudate revealed polymorphonuclear leukocytes with Gram-negative and Gram-positive diplococci which were located predominantly outside the cells. Four blood cultures and cultures of the urethral exudate and urine sediment were negative for organisms. Darkfield examination of the penile lesion was not carried out. A VDRL test was negative. Routine blood chemical determinations, an x-ray film of the chest and an electrocardiogram were all within normal limits. Penicillin was administered intravenously for ten days and the patient had an uncomplicated recovery.

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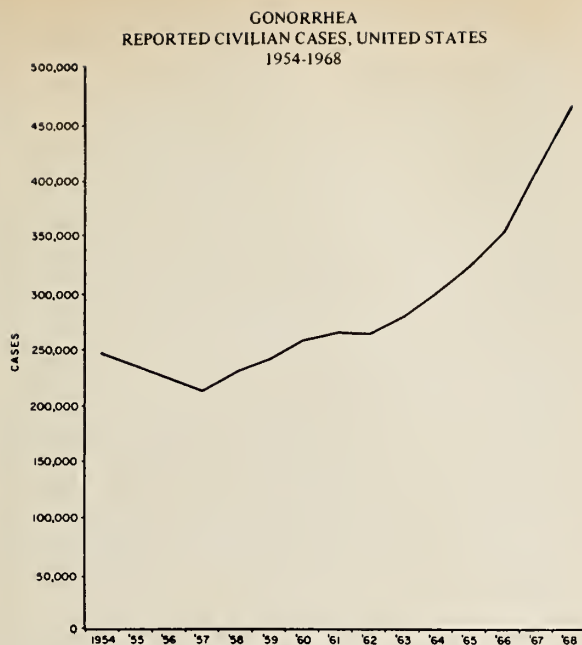


Chart 1.—Reported cases of gonorrhea in the civilian population between 1954 and 1968. (Reproduced by permission of the publisher.<sup>3</sup>)

DR. EDELMAN: The case will be discussed by Dr. Drutz.

DR. DRUTZ: \* The patient, a young man who experiments with drugs and is sexually promiscuous, is typical of many who are likely to have gonorrhea in our prevailing social climate. We did not isolate the gonococcus from this patient, but the clinical course was sufficiently distinctive to permit the diagnosis of gonococcal sepsis. Gonococcal organisms were recovered from two other patients recently admitted with gonococcal sepsis and arthritis.

Gonococcal sepsis and arthritis have been relatively infrequent problems since the inception of the antibiotic era. Yet these three patients were seen at Moffitt Hospital within a 14-day period. In this regard, it is well to bear in mind that this hospital is largely a diagnostic referral center. Dr. Austin Brewin of San Francisco General Hospital has informed me that three cases of gonococcal arthritis a month is not at all unusual at that institution. Thirty-six years ago, Myers and Keefer<sup>1</sup> pointed out that gonorrhea was one of the most common causes of acute and chronic arthritis. While we have not regained this pinnacle in 1970, we seem to be rapidly approaching it. As a recent editorial in the *Annals of Internal Medicine* indi-

cated, "by any standards, gonorrhea is out of control in the United States."<sup>2</sup>

## The Resurgence of Gonorrhea

Shown in Chart 1 are the reported cases of gonorrhea in the civilian population between 1954 and 1968.<sup>3</sup> In this 15-year period, the number of cases doubled. However, a survey of private physicians published in 1963 revealed that 70 percent of gonococcal infections are treated outside of public clinics and that only 10 percent of these are ever reported.<sup>4</sup> Thus, the true incidence of gonorrhea in the United States is unknown, but conservative estimates indicate that 1.7 million new cases occur in this country every year.<sup>2</sup> The reasons for the resurgence of gonorrhea are complex and closely interrelated.

*Short Incubation Period.* With an incubation period of only three to five days, gonorrhea becomes highly infectious almost immediately.

*High Communicability.* Virtually every intimate sexual contact involving a patient infected with gonorrhea places the infecting agent in an ideal site for multiplication in the new host, namely a mucosal surface.

*Asymptomatic Carrier.* The carrier state is an extremely important mechanism by which gonorrhea is perpetuated in a population. Women are a particular problem in this regard because they may have neither urethritis nor even a vaginal discharge, and therefore may unknowingly harbor and transmit the gonococcus. Indeed, direct swabs from normal-appearing, but infected, cervixes can transmit gonorrhea to male volunteers.<sup>5</sup> Asymptomatic gonococcal carriage in males has been far less frequent and symptoms of urethritis generally prompt medical consultation. However, a few cases have been documented,<sup>6</sup> and asymptomatic gonococcal infection in the rectum of male homosexuals is an increasingly important source of dissemination of the microorganism.<sup>2</sup>

*Absence of Immunity.* Gonorrhea is not an infection which confers significant immunity upon its victims, and therefore repeated infections are common.

*Changing Sexual Mores.* There has been a change in sexual attitudes in the Western world with the advent of birth control pills and a generally more permissive moral climate. This change is reflected in the high incidence of gonorrhea in teenagers.<sup>7</sup> Yet, if sexual permissiveness were the

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major reason for the upsurge of gonorrhea, there should have been an equivalent rise in primary and secondary syphilis.<sup>2</sup> This has not been the case. Again the aspect of communicability arises, for whereas a large proportion of patients with syphilis are asymptomatic, most are non-infectious. By contrast, even the asymptomatic carriers of the gonococcus are highly infectious.

*Inadequate Identification of Contacts.* It became apparent as early as 1947 that the reduction in syphilis morbidity in response to penicillin was proportionately much greater than the reduction of morbidity in gonorrhea. Efforts to deal with gonorrhea were reinforced, and in 1952 a system known as "speed zone epidemiology" was introduced. With this technique, male patients were interviewed, and every effort was made to examine and treat their contacts within 72 hours. In 1956 "antibiotic quarantine" was added. Here, contacts were treated with benzathine penicillin G to maintain prolonged blood levels in an attempt to prevent reinfection for two to six weeks.<sup>7</sup> Unfortunately, as we shall see, the low blood levels of penicillin produced by regimens of this type may tend to select out relatively penicillin-resistant gonococcal strains.

Despite enthusiastic application of these techniques, the incidence of gonorrhea was not significantly reduced. Cases simply cannot be found and treated as fast as they occur. A further obstruction to case finding is the absence of a practical diagnostic serological test for gonorrhea.

*Decreasing Penicillin Sensitivity of the Gonococcus.* There has been a progressive decrease in the susceptibility of the gonococcus to penicillin.<sup>8</sup> This is particularly apparent in Southeast Asia, where prostitutes have been shown to harbor gonococcal strains which are relatively resistant to penicillin. However, the same trends have been observed in the United States, particularly on the West Coast. A contributing factor to the problem in the Orient may be the relative ease with which antibiotics are obtained. Indeed, prostitutes often treat themselves continuously with low doses of antibiotics as prophylaxis against venereal infection. Under these conditions, drug use only assures the selective acquisition of gonococcal strains that are more resistant to penicillin.

In order to understand precisely what is meant by a resistant gonococcus, it should be appreciated that group A beta-hemolytic streptococci are generally sensitive to 0.02 mcg per ml of penicil-

lin, pneumococci to 0.04 mcg per ml, and non-penicillinase-producing staphylococci to 0.4 mcg per ml. From 1945 to 1954, most gonococci were sensitive to 0.03 mcg per ml of penicillin. In 1955 nearly one-fourth of strains required 0.06 to 0.12 mcg per ml for inhibition. By 1964 strains were requiring up to 0.6 mcg per ml, and in 1969 some gonococcal isolates required up to 2.0 mcg per ml of penicillin for inhibition although most strains were still sensitive to 0.3 mcg per ml.<sup>7,9</sup>

It should be emphasized that the penicillin resistance to the gonococcus is purely relative and does not indicate that this antibiotic is no longer useful in treating gonorrhea. What it does indicate is that the favored single-shot outpatient treatment for gonorrhea may no longer be practical as larger and larger doses of penicillin are required to achieve therapeutic levels in the body.<sup>8</sup>

## The Local Manifestations of Gonorrhea

Depending largely upon the sexual proclivities of the patient, gonococci may be introduced into the body in a variety of sites. The distinct propensity of the gonococcus to invade mucosal surfaces and the general resistance of squamous epithelium to infection account for the usual symptoms of gonorrhea. In males, symptoms of urethritis with burning on urination and penile discharge are the usual initial manifestations of infection. Urethritis may develop in females also, but they more frequently harbor the gonococcus asymptotically or have varying degrees of vaginal discharge. In patients who engage in anal intercourse, proctitis may be the presenting problem.<sup>9</sup> It is likely, however, that gonococcal proctitis is often asymptomatic. Patients engaging in oral-genital relationships may present with pharyngitis of some severity.<sup>10,11</sup> It is clear that gonorrhea must at least be considered in the differential diagnosis of any sore throat, and that Gram-negative diplococci in the pharynx cannot be dismissed as *Neisseria catarrhalis*, or indeed *Neisseria meningitidis*, without appropriate bacterial culture data. Conjunctivitis is a well-known manifestation of ophthalmia neonatorum, developing when a newborn infant has passed through a gonococcus-infected birth canal. It is not generally appreciated that the anogenital orifices may also be infected by the same mechanism, and that infants may go on to have gonococcal sepsis and arthritis.<sup>12</sup>



## Progressive Infection

In males who do not seek medical attention, the initial acute anterior urethritis spreads to involve the posterior urethra, resulting in frequency and urgency of urination, and terminal hematuria. Columnar epithelium lining the urethral glands, prostatic ducts, prostate, seminal vesicles, vas deferens, and epididymis (as well as the anterior urethra) is especially vulnerable to invasion by the gonococcus. As infection spreads posteriorly, perineal discomfort occurs. There may be acute urinary retention as the prostate and seminal vesicles are invaded, and acute seminal vesiculitis may be complicated by high fever and pain in the suprapubic, inguinal and sacral areas. With invasion of the epididymis, testicular swelling and pain develop. In the absence of treatment, there is a tendency to chronicity with progressive tissue destruction. This is the situation which predisposes to formation of urethral strictures.

In females there may be remarkably few symptoms so long as the infection is localized to the lower genitourinary tract. The spread of gonococci from the cervix to the fallopian tubes, however, is generally accompanied by severe lower abdominal pain and pelvic peritonitis. It is this sequence of events which is termed acute pelvic inflammatory disease (PID). Repeated bouts of infection may result in marked tissue destruction with formation of abscesses, tubal strictures, and ultimate loss of fertility. Chronic PID may be a source of considerable pain and disability.

## Extragenital Manifestations

The extragenital manifestations of gonorrhea are the result of gonococcal bacteremia and reflect the affinity which the gonococcus appears to hold for serosal and synovial surfaces. The exact incidence of bacteremia in patients infected with the gonococcus is unknown, but appears to be quite low. Even patients with clear evidence of bacteremic disease, such as skin lesions or arthritis, may have only a 15 percent chance of having a positive blood culture.<sup>13</sup>

It is essential to appreciate that gonococcal bacteremia and its complications may occur in the presence or absence of overt genital infection. In females sepsis may evolve from an asymptomatic carrier state following menstruation, pregnancy or unusual sexual stimulation.



**Figure 1.**—Gonococcal skin lesions. The larger lesion is a characteristic hemorrhagic papule. Overlying the distal interphalangeal joint is an erythematous macule containing a central pustule which has ruptured.

It has followed vigorous prostatic massage in males. Further, gonococcal sepsis has been documented following prostatectomy or hysterosalpingectomy in elderly patients in whom gonococci have apparently been dormant for years.<sup>14,15</sup>

Skin lesions and arthritis are the most common extragenital manifestations of gonococcal septicemia; however, several other manifestations will also be discussed.

**Skin Lesions.** Gonococcal skin lesions are usually widely distributed, sparse (seldom more than a dozen), and tend to occur on the distal portion of the extremities, especially around joints.<sup>16</sup> The initial lesion is a pinpoint erythematous macule (Figure 1) which rapidly evolves into one of three characteristic patterns:<sup>17,18</sup>

- Vesicles or pustules located centrally on a broad erythematous base
- Hemorrhagic papules (Figure 1)
- Hemorrhagic bullae

The lesions are typically tender and reveal the

TABLE 1.—Summary of Clinical Features in 140 Cases of Gonococcal Arthritis\*

1. Sex		
Males	104	
Females	36	
2. Polyarthritis	107	
Monarthritis	33	
3. Joints Involved		Tenosynovitis
Knees	127	4
Ankles	56	32
Wrists	44	19
Metacarpophalangeal	27	6
Shoulders	25	
Metatarsal and laryngeal	27	6
Fingers	31	4
Hips	23	
Elbows	20	
Lumbar part of spine	14	
Toes	19	
Sacro-iliac	8	
Heels	7	
Cervical part of spine	6	
Dorsal part of spine	4	
Sternoclavicular	3	
Costosternal	2	
Temporomandibular	3	
Olecranon bursa	1	
Acromioclavicular	1	
4. Associated Features		
Conjunctivitis	21	
Abscess of tendon sheath	2	
Death	7	
Endocarditis	2	
Glomerulonephritis	1	
Intercurrent pneumonia	3	
Progressive gonococcal infection	1	
Iridocyclitis	4	
Glomerulonephritis	2	
Pregnancy	4	
Bacteremia	5	
Recovered	3	
Died	2	
Endocarditis	2	
Keratoderma blennorrhagicum	4	
Sterile meningitis	1	

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presence of vasculitis histologically. Gonococci can rarely be cultured from these lesions. A paper by Ackerman and associates<sup>17</sup> contains especially good color photographs of typical gonococcal skin lesions. In the absence of therapy there is a small, but distinct, propensity for gonococcal skin lesions to recur in crops. Indeed, there may be a striking similarity to chronic meningococcemia in this regard.<sup>17</sup> However, the combination of focal hemorrhagic and vesiculopustular lesions in a patient with fever and arthritis is highly suggestive of gonococcemia.

*Arthritis.* Arthritis is perhaps the most widely appreciated extragenital manifestation of gonorrhea. It has been emphasized that the clinical presentation of gonococcal arthritis has changed in recent years. "What was once a relatively common complication of genital gonorrhea that predominantly affected males and left a large proportion of patients with residual joint disability now seems to be a relatively uncommon disease occurring principally in females and responding dramatically to penicillin with no residual joint damage."<sup>19</sup> The change has likely been wrought by the advent of effective antibiotic therapy. When urethritis develops in males they usually seek early medical attention, and the disease is aborted before systemic infection can develop. On the other hand, females with asymptomatic genital infections often do not see a physician until systemic manifestations of gonorrhea have developed. The arthritis is, however, very responsive to treatment with penicillin.

Although the severest arthritic manifestations of gonorrhea may be localized to one or two joints, gonococcal arthritis at its inception is characterized by polyarthralgias or frank polyarthritis. These findings suggest that multiple joints are initially infected but in only a few does progressive disease develop. Alternatively, it has been suggested that the polyarthritis is a hypersensitivity phenomenon to products of the gonococcus.

Table 1 summarizes the clinical features of 140 cases of gonococcal arthritis seen by Keefer and Spink<sup>20</sup> at the Boston City Hospital before the beginning of the antibiotic era. It is apparent that virtually any joint in the body may be involved, but the knees, ankles, and wrists most commonly. An extremely important clue to gonococcal arthritis is the presence of tenosynovitis around the wrists, ankles, metacarpophalangeal joints, and knees. The associated tenderness is so great that the patient may not voluntarily move the joint or allow it to be touched. Occasionally, tendon sheaths may be involved without associated arthritis. Presumably the gonococcus invades the tendon sheaths; abscesses have been observed in these sheaths.

Synovial fluid examination generally reveals polymorphonuclear leukocytosis. It has been said that white cell counts greater than 30,000 cells per cu mm are usually associated with positive joint fluid cultures, while counts below this value



occur with sterile fluid.<sup>21</sup> There are, however, exceptions to this general rule. Even in the best of circumstances (joint fluid dripped directly on a chocolate agar plate and immediately placed in a CO<sub>2</sub> atmosphere) only 25 percent of joints reveal the gonococcus.<sup>13,20</sup>

There appears to be a distinct relationship between the duration of arthritis and the ability to recover the gonococcus from joint fluid. The result is that two syndromes of gonococcal arthritis can be recognized. In the first, arthritis occurs in a setting of acute illness and is accompanied by chills, fever and skin lesions. Joint effusion is not pronounced and synovial fluid cultures are usually negative, while blood cultures are more frequently positive. In the second form of gonococcal arthritis, bacteremia is asymptomatic, skin lesions are absent, and blood cultures are seldom positive. Joint effusion may be pronounced, and synovial fluid cultures are more likely to be positive. The explanation for this difference is presumably that patients symptomatic from gonococcal bacteremia seek medical care relatively early, before joint disease is well established. In contrast, patients with asymptomatic bacteremia usually do not consult a physician until they have persistent arthritic symptoms and for that reason are more likely to have positive joint fluid culture, more time having passed for bacterial multiplication.<sup>19</sup>

**Conjunctivitis and Iridocyclitis.** It is not generally appreciated that gonococcal sepsis may be accompanied by conjunctivitis or frank iridocyclitis. Keefer and Spink<sup>20</sup> reported that "metastatic catarrhal conjunctivitis," characteristically culture-negative, occurred in 10 to 20 percent of their patients with gonococcal arthritis. It appeared to be more commonly associated with negative than positive joint fluid cultures.

**Endocarditis.** Gonococcal endocarditis is no longer common, but it received a great deal of attention in the literature of the preantibiotic era. Unlike patients with other gonococcemia-related syndromes, those with endocarditis may be extremely ill with fulminating sepsis.<sup>22</sup> One characteristic by which gonococcal endocarditis might be suspected is the presence of two fever spikes a day—the so-called double quotidian temperature curve.

**Meningitis.** As of 1963, 26 cases of gonococcal meningitis had been reported in the medical literature.<sup>23</sup> It is possible that this diagnosis is

missed when Gram-negative diplococci seen in the cerebrospinal fluid are automatically assumed to be *Neisseria meningitidis*.

**Perihepatitis (FitzHugh-Curtis syndrome).** Gonococcal perihepatitis has been classically considered a rare complication of gonococcal infection in females wherein microorganisms spread directly from the pelvis over the peritoneal surface of the liver. Symptoms include right upper quadrant abdominal pain, pleuritic in character and often referred to the shoulder, as well as tenderness, guarding, and a friction rub over the liver. The latter is not always present, but may be of great diagnostic value.<sup>24</sup> As symptoms of genitourinary gonorrhea may be minimal or absent, operation for acute cholecystitis may be needlessly performed. The "violin string" adhesions between the anterior abdominal wall and the liver which have been found in patients with known gonococcal pelvic infection are a reflection of this process. Recently the FitzHugh-Curtis syndrome was recognized for the first time in a male.<sup>25</sup> In this patient the gonococcus was isolated from histologically normal-appearing liver tissue. This perihepatic infection may have resulted from either bacteremia or from retroperitoneal lymphatic spread from the patient's genital gonorrhea.

**Other Sites.** Although rare today, a wide variety of metastatic complications of gonococcal infection have been reported, including liver abscesses, myositis, osteomyelitis, chondritis, pericarditis, myelitis, pleurisy, and pneumonia.

## Diagnosis

The diagnosis of gonococcal sepsis rests in large part upon recognition of the clinical syndromes with which extragenital disease is associated, since culture of the gonococci from blood, skin or joints may be quite difficult. Demonstration of gonococci in genital tissues provides valuable supportive evidence for a diagnosis of gonococcal sepsis. In males with urethritis, the presence in urethral discharge of Gram-negative, kidney bean-shaped diplococci within polymorphonuclear leukocytes provides presumptive evidence for the diagnosis.<sup>9</sup> When the microorganisms are numerous, cultures will usually be positive. A negative smear does not mean that urethritis is non-gonococcal in origin, and cultures may on occasion grow gonococci.



Swabs of the anal canal in homosexuals or of the female genitalia will generally yield a variety of microorganisms in large numbers, obscuring the gonococcus even if present. Furthermore, asymptomatic carriers of the microorganism may have very few gonococci demonstrable. Finally, smears may be falsely positive for gonococci. In this regard, Garson and Thayer<sup>9</sup> found saprophytic *Neisseria* in 3.4 percent of women not infected with *Neisseria gonorrhoeae*.<sup>9</sup> In these circumstances, culture of the anal canal in the male and female, and culture of the female genitalia are required. Culture of the cervical os will probably detect about 82 percent of infected women.<sup>9</sup> However, up to 7 percent may harbor the gonococcus in the posterior vaginal fornix,<sup>26</sup> and up to 10 percent only in the rectum.<sup>8</sup> Therefore, culturing of the female with suspected gonorrhea can be considered to be complete only when material from the cervical os, the posterior vaginal fornix and the anus have been cultured. Urethral cultures appear to be relatively unproductive in females.<sup>27</sup> On occasion, culture of the spun urine sediment for gonococci may disclose the microorganisms in men or women.

The development of the highly selective Thayer-Martin<sup>28</sup> medium has assisted in the isolation of gonococci from specimens contaminated with a variety of microorganisms. This medium incorporates vancomycin, colistin, and neomycin which effectively inhibit the growth of nearly all microorganisms except oxidase-positive *Neisseria gonorrhoeae* and *Neisseria meningitidis*. It is currently believed that the growth of typical Gram-negative, oxidase-positive diplococci on Thayer-Martin medium suffices for the identification of the gonococcus. Carbohydrate fermentation reactions are reserved for positive identification of isolates from blood, conjunctiva, or synovial fluid or in instances where medico-legal considerations may occur.<sup>9</sup>

Other diagnostic aids for gonorrhea are also in use.<sup>9</sup> A fluorescent antibody test has been developed for detecting gonococci on direct smears of suspected positive exudates. A delayed fluorescent antibody test has also been utilized to examine material cultured for gonococci after a period of growth under carbon dioxide. Staining with fluorescent-tagged antigenococcal serum provides rapid identification of the microorganism and shortens the usual period required for conducting sugar fermentation reactions.

The current status of serological testing for gonorrhea has been reviewed recently.<sup>29</sup> The search continues for an adequate serological test. The literature of the 1930's and 1940's placed considerable emphasis on a gonococcal complement fixation test which was in common use at that time.<sup>1,15</sup> It is now appreciated that this test is not specific and that titers remain elevated for long periods of time after infection.

## Treatment

Penicillin is the treatment of choice for gonorrhea and its extragenital manifestations. A daily dose of 5 to 10 million units of aqueous penicillin administered intravenously at intervals or by continuous infusion for a total of 10 to 14 days should suffice to treat gonococcal arthritis. Because penicillin crosses the inflamed synovial membrane quite efficiently, there is no need for intra-articular administration of the drug.<sup>30</sup> Indeed, penicillin is irritating to the joint space when introduced in this manner and may induce a chemical synovitis. The response of gonococcal arthritis to penicillin is generally so dramatic that it has been considered a diagnostically useful test.<sup>21</sup> The response is not always so rapid, however, and it has been emphasized that joint effusion may remain for some time after completion of therapy.<sup>21</sup> However, there is no question that penicillin has prevented the profound joint destruction and crippling which characterized gonococcal arthritis before the antibiotic era.

For patients with gonococcal sepsis who are allergic to penicillin, useful alternatives include cephalosporin derivatives (although a certain proportion of penicillin-allergic patients will also be sensitive to these drugs), tetracycline, or erythromycin.

DR. EDELMAN: Has anyone looked into the possibility that the birth control steroids might in some way alter the immunological response to the gonococcus?

DR. DRUTZ: I am not aware of any studies which have indicated that birth control pills have altered gonorrhea, except perhaps by lowering inhibitions toward sexual intercourse.

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## DETECTING AIRWAY OBSTRUCTION

"Spirometry is the most common and the easiest means of detecting airway obstruction in a patient you suspect has one of the obstructive airway diseases. But I offer two warnings about its use: first, make certain that you have an abnormality, in the form of slowing of air flow on exhalation, which is irreversible. In other words, be sure that it does not respond to a bronchodilator significantly. Second, one examination, one spirometric determination, is not adequate for making the proper diagnosis. One should have this repeated because the next examination occasionally shows that the patient does not have airway obstruction at all."

—HAROLD A. LYONS, M.D., Brooklyn  
 Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Important Advances in Clinical Medicine

## *Epitomes of Progress -- Orthopedics*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Total Hip Replacement

In 1958, Charnley, realizing the need for a more reliable hip arthroplasty, began using self-curing methyl methacrylate as a "cement" to hold the acetabular and femoral components. The methyl methacrylate is used as a grouting, filling the interstices within the bone and thereby providing a hold for the mechanical components.

Although acrylic has been used for many years in endoprotheses, the present use requires polymerization within the body and is considered by the Food and Drug Administration to represent a new utilization of the material and, as such, to require a Claim for Exemption for a New Drug.

The components of a total hip replacement are a metallic femoral head prosthesis with a socket of either high density polyethylene, or the metal used in the prosthesis. The components are in-

serted separately, each being "cemented" into the prepared area. The results, to date, have been most encouraging; the procedure providing excellent motion and pain relief. There are, however, definite risks entailed in the utilization of acrylic as a cement. The free monomer, which is mixed with the polymer, is toxic to the liver, kidney and heart of animals, and is probably responsible for the transient hypotensive episodes that occasionally occur following introduction of the material. Also, many surgeons performing the procedure have noted increased incidence of wound infection. As a consequence, great interest has developed in clean air operating rooms employing filtering systems which have the ability to remove bacteria and dust from the air.

Although generally believed to be the most significant advance in orthopedic hip surgery, it



is probable that total prosthetic replacement for advanced exarthrosis as developed by Charnley and others, may be but the forerunner of further advances in the field of total joint replacement.

THEODORE R. VAUGH, M.D.

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### Surgical Treatment of Rheumatoid Arthritis in the Hands

Less than one third of patients having rheumatoid arthritis may be helped by surgical operation. Destruction of the wrist, small joints and tendons of the hand can be arrested by excising thick, granulomatous synovium. Synovectomy may relieve pain and prevent subsequent deformity, but often results in some limitation of motion.

Rheumatoid synovium surrounding the flexor tendons beneath the transverse carpal ligament frequently causes compression of the median nerve, resulting in the so-called carpal tunnel syndrome. Surgical excision of the synovium, thereby decompressing the nerve, usually will relieve symptoms of the syndrome. The function of extensor and flexor tendons that rupture may be restored by tendon transfers or grafts.

Destroyed, subluxed or dislocated metacarpophalangeal joints are frequently accompanied by ulna drift of the fingers. Relocation of the extensor mechanism over the center of the metacarpophalangeal joints after arthroplasty of these articulations usually results in improved position and function. Prosthetic replacement of severely destroyed joints, especially at the metacarpophalangeal level, with implants made of silicone rubber seems to be gaining acceptance.

PAUL R. LIPSCOMB, M.D.

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Niebauer JJ, Shaw JL, Doren WW: The silicone-dacron hinge prosthesis: design, evaluation and application. *Proceedings ASSH J Bone Joint Surg* 50A:634, 1968

### The Use of Compression Plates for Fractures

Compression plating of fractured long bones has now become an accepted part of the fracture surgeon's armamentarium. The method was devised by Professor Müller of Basle and a group of his colleagues. The plates are thicker and heavier than previously designed plates, with firm fixation to the bone by screws. The plate is fixed to one fragment of the fractured bone, reduction is achieved and a device is used to compress the fracture fragments together; then the plate is fixed to the other fragment. The method demands a clear understanding of various approaches to long bones and excellent surgical technique. Also, one should be familiar with the instrumentation and whole procedure before operating upon a patient. With anatomical reduction, healing takes place directly across the fracture site in the cortices, and resorption of bone has not been a problem. Normal vascularization can occur through the medullary canal.

The plates and fixation are strong enough so that no immobilization is used in fractures of the forearm and often not in the lower extremity, although balanced suspension is used for the first two weeks postoperatively. Although the plates are devised for all bones, we find their greatest use for fresh fractures in the forearm for non-union of forearm bones and humerus and rarely in comminuted fractures of the femur or non-union. We have not used them for fresh fractures in the tibia; rarely in non-union. When used in the lower extremities, weight-bearing should not be permitted for three months or longer. We would like to emphasize that excellent surgical technique is necessary, wide experience is demanded, and familiarization with the apparatus is a requisite for using the method upon a patient.

J. PAUL HARVEY, JR., M.D.

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Müller ME, Allgower M, Willenegger H: *Technique of Internal Fixation of Fractures*. New York City, Springer-Verlag, New York, Inc., 1965

## New Concepts of Sterile Conditions in the Operating Room

There has always been great concern to reduce the bacterial count in the operating room and thus minimize infections arising from surgical procedures. Recently there has been an increase of interest in this idea, mainly stimulated by Charnley's work at Wrightington Hospital, England, in which he uses a total hip replacement and methylmethacrylate. Initially when this operation was done, the infection rate was fairly high. The results of such infection were often disastrous due to the extensive amount of foreign material utilized. Charnley developed a "green room" in which filtered air at great velocity was run through the operating suite. The theory proposed was that the clean air would wash out the particles on which pathogenic bacteria rest.

The need for clean rooms that developed in the course of the aerospace program led to the production of special filters and technologic advances which show promise in helping to reduce the level of infection in operating suites.

A great deal of salesmanship and sales promotion has accompanied the introduction of the new laminar air flow units. There are great differences of opinion about various factors in these units—the type of laminar air flow (whether it is horizontal or vertical), the total operating room garb for the surgeon and other personnel, and whether or not large amounts of suction should be used.

Undoubtedly microbiologists will assume a major role in planning and developing better operating room conditions for the future.

VERNON L. NICKEL, M.D.

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## Unstable Knee

In 1950, the concept of early repair of acute ligamentous injuries of the knee was put forth. This principle has become well established in the two decades since then. In 1966, further guidelines were provided by a systematic classification

of ligamentous sprains based on degree of severity.

Surgical intervention is indicated for "severe" sprains with complete disruption of continuity and instability (Group III). Protection for several weeks is indicated for the "moderate" sprains with partial tearing and no instability (Group II). Symptomatic treatment is indicated for the "mild" sprains with minimal tearing and no instability (Group I).

The combination of early definitive diagnosis and expeditious definitive treatment insures the most optimal results and the most rapid return to previous activity.

MARTIN E. BLAZINA, M.D.

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O'Donoghue D: Treatment of Injuries to Athletes. Philadelphia, WB Saunders Company, 1970

## Ambulatory Treatment of Legg-Calves-Perthes Syndrome

The aim of treatment in the Legg-Calves-Perthes Syndrome is the prevention of deformity of the femoral head. It is now generally accepted that positioning the affected hip in abduction and internal rotation, combined with an aggressive exercise program, most effectively accomplishes this goal. This position best contains the femoral head (particularly the involved anterior portion) within the acetabulum and allows reconstitution of a spherical head with the least residual deformity.

An excellent guideline during treatment is observation of the degree of subluxation of the femoral head from the medial wall of the acetabulum (increased femur-teardrop distance as seen on antero-posterior x-ray films). If the femur-teardrop distance is increased, a concentric articulation of the femoral head and acetabulum cannot exist unless deformity of the femoral head is present. Therefore, early reduction of the femur-teardrop distance to normal (1.0 cm or less) and maintenance of the reduction is a major treatment objective.



It is now recognized that most children under five years old require no treatment other than restriction of activities and careful observation, as significant subluxation rarely occurs and the healing process is rapid (particularly in the cases with partial head involvement).

Treatment is indicated for older children or those with significant subluxation, where the desired position of abduction and internal rotation is probably best achieved and maintained by bilateral leg casts and crossbar as advocated by Craig, Petrie, Harrison, and others; but a variety of braces have also been used (generally less effectively). A child may safely weight-bear without increasing deformity of the head when no subluxation is present (normal femur-teardrop distance), and there is reossification of the posterior portion of the epiphysis (seen on the frog lateral view). Maintenance of this position will commonly be required for two years or longer, to allow adequate healing of the epiphysis.

In recent years, surgical operations such as femoral or iliac osteotomy have been used successfully to improve the prognosis and shorten the treatment time in the older child. When an optimum result is desired in a hip with persistent subluxation or considerable enlargement of the femoral head, consideration should be given to referral for evaluation for such surgical treatment.

STANFORD M. NOEL, M.D.

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### Recent Advances in the Treatment of Arthritis of the Knee

Definite relief of pain has been shown after corrective osteotomy in patients with arthritis in one compartment of the knee. Recently reported series corroborate earlier reports that the majority of patients with painful arthritic knees and nar-

rowing of either compartment could obtain long-term benefit by restoring alignment and balancing the weight-bearing forces to the more normal side.

The operation is indicated when adequate conservative measures fail to control the progression of the disease, particularly in patients with degenerative joint disease but also in selected cases of rheumatoid knee. Poor results occurred with unstable knees and advanced generalized knee arthritis. The procedure is technically not difficult, the complication rate is low, and loss of motion or delayed union was not a problem.

Early osteotomy has benefited the patient in most instances and does not foreclose opportunity for future arthroplasty when suitable endoprostheses become available.

PHILLIP H. HAY, M.D.

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### Treatment of Fractures of the Leg by Modified Casting and Early Weight-Bearing

A healing wound requires stress for the proper deposition of collagen—be it a laceration, hernia repair, or fractured bone. Lower extremity fractures and their associated soft tissue injuries heal best when subjected to early weight-bearing within physiological limits. Fractures of the tibia are treated by applying a snug, well molded long leg cast with the knee in extension, and then encouragement of progressive weight-bearing. After femoral shaft fractures are healed sufficiently in traction so they no longer displace, a cast brace consisting of open ended quadrilateral socket and knee joints fixed in plaster is fitted and progressive weight-bearing is then begun.

PHILIP H. REISWIG, M.D.

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## Immediate Postsurgical Prosthetic Fitting For Lower Extremity Amputations

Experience since 1964 with the immediate application of prosthesis to persons having amputations at any level below the hip has shown this procedure to result in healthier stumps, more rapid healing and a reduction in the postsurgical pain and hospital time. Because of these benefits, those amputations performed for peripheral vascular disease, with or without diabetes, have resulted in the salvage of more knees than was possible with conventional amputation techniques.

The procedure consists of application of a plaster cast covering the stump and proximal limb at the operating table at the conclusion of operation. To this is affixed an adjustable aluminum pylon prosthesis incorporating a prosthetic foot. Ambulation is begun, partial weight bearing usually one

day postoperatively and a permanent-type prosthesis is fitted on the average of 28 days postoperatively.

To meet the interest in the new technique, three universities who offer prosthetic courses, namely New York University, Northwestern University and the University of California at Los Angeles, have introduced courses in immediate postsurgical prosthetic management including the special surgical and prosthetic techniques involved.

C. DAVID PETERSEN, M.D.

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## CMA and the Medical Schools

THESE ARE TIMES OF GREAT and fundamental changes in medical education and medical practice. Many of the old assumptions and beliefs are being questioned. New assumptions, attitudes and expectations are making new demands upon both medical education and medical practice. Neither "town" nor "gown" is yet entirely clear just how these demands are best to be met. Precise documentation of what is needed is absent. A realization is growing that a substantial number of these unsolved problems are shared alike by medical schools and by organized medicine.

This community of interest is brought into focus by a recent action of the California Medical Association Commission on Legislation. The Commission has invited suggestions and expressions of attitude from the medical school deans for consideration in preparing CMA's 1971 legislative program, both with respect to the needs of the medical schools and the posture CMA should take on statewide issues. As far as we know, this action is unprecedented. It could lead to a new cooperation and a better informed approach to many health problems. This should serve the government and the people of this state very well indeed.

Liaison between CMA and the eight medical schools in this state is nothing new. Many members of this association may not be fully aware of the extent to which this has been developed over the last decade or so. We know of nothing comparable to it anywhere in the nation. Many years ago a Liaison Committee to Medical Schools was created for the purpose of resolving the then more frequent problems of potential or actual misunderstanding between "town" and "gown." This committee continues to function and serve its purpose. But the liaison has gone far beyond this. Deans, faculty and students have all become increasingly involved in CMA activities.

The deans are regularly invited to the Council's meetings and to speak. They are provided with agenda and minutes. They are warmly welcomed and usually a number are present. Two deans have been particularly active in association affairs, and a coterie of assistant and associate deans contribute substantially. This liaison proved particularly important when the deans, the CMA, the California Hospital Association, the Department of Public Health and others got together, and through their collaborative efforts made California's Regional Medical Programs one of the most outstanding in the nation.

Faculty members from the medical schools have served on various CMA committees over the years and some have served in the House of Delegates. Many more have participated in CMA institutes and postgraduate courses for the continuing education of physicians throughout the state. With the more recent advent of the Scientific Board and its various scientific committees this faculty contribution to the scientific purpose of CMA increased and achieved its present very significant level when the Advisory Panels to the eighteen Scientific Sections of the Scientific Assembly came into being. One is just beginning to see what can and is being accomplished as the resources of the medical school faculties are more closely brought to bear upon the scientific activities of the CMA. Each Advisory Panel includes a member from the appropriate department of each of the eight medical schools as well as representatives from the Scientific Sections and from the various scientific specialty societies recognized by the Council. Among the results already visible are innovative and improved programs at the CMA Scientific Sessions, and the timely epitomes of important advances in clinical medicine in each specialty which have now become a regular feature in CALIFORNIA MEDICINE.

Liaison at the student level has also existed for many years. More recently the Committee on the



Role of Medicine in Society has played a central role. The student body in each of the eight California medical schools designates a representative who serves on this committee. He acts as the primary liaison between the CMA and the students in his school. These students attend the AMA House of Delegates meetings and have been welcomed there by the California delegation. They have spoken their thoughts in AMA reference committees and in the delegation caucuses. Plans are afoot for similar student representative participation at the CMA Annual Meeting in March. In addition, twenty or more other CMA committees have invited student participation and have welcomed students who, incidentally, were selected by the students themselves from applicants who were interested in the subject matter. And not to be overlooked is the "Bridge the Generation Gap" program of CALIFORNIA MEDICINE which, with substantial help from the Woman's Auxiliary, is at present providing 860 subscriptions to this journal to medical students.

Now that many problems will be shared, the liaison traffic between town and gown should be equal both ways. Organized medicine at its higher levels should be as willing to participate where needed in medical school affairs as the deans are to help in advancing programs of the medical association. And at grass-roots a balancing of somewhat reverse order is needed; more full-time faculty members should join in the work-a-day chores of local medical societies, through membership and active participation, just as unpaid "town" physicians give their time and services to teach medical students and help supervise the care of medical center patients. As the ivory towers and their scholarly inhabitants find themselves increasingly awash in the problem-ridden mainstream of medical care, it is essential that they become much more involved in what it to be done about these problems. It is not too soon for this involvement to start. The course of the stream, even its content, is undergoing fundamental change. It can still be directed. The invitation of the CMA Legislative Commission is already being heeded by the medical schools and others. It could be the beginning of a great new cooperative effort in the professional and public interest.

## Adam and Eve

ACCORDING TO THE BIBLE, Eve was a chondral extension of Adam; at least since that time, man has wondered about the differences between the sexes, and innumerable ones, currently very unfashionable to assert, have been recognized. From the endocrine viewpoint, the primary male-female difference is in the amount and ratio of androgens and estrogens produced. Since androgen is an obligatory intermediate for estrogen biosynthesis, and since both ovary and testis make the same hormones, the essential sexual differences are regulatory ones—(1) how much androgen to make and (2) whether to leave it primarily as such or to convert it to estrogen.

Gonadal differentiation in the embryo is determined by the nature of the second sex chromosome; if this is a Y, a testis develops, and if it is an X, an ovary.<sup>1</sup> A locally active testis substance called the "inducer" then acts to suppress the development of the female duct primordia which would otherwise give rise to the uterus and Fallopian tubes. From that point forth, all of differentiation depends not on genetic sex but on the presence or absence of potent androgens. The Wolffian ducts develop into the vasa, seminal vesicles, and epididymes, and the external genitalia masculinize because of androgen hegemony. That is, the genital structures are not genetically male or female, but assume male patterns because of a positive influence of the male hormones derived from the testis.

A similar role of androgen has been shown in establishing the difference between the male and female brain in their stimulation of production of gonadotropin. Specifically, males produce gonadotropin in an acyclic manner, whereas normal females release gonadotropin in a cyclic manner which results in estrus or menstrual cycles. This difference is not in the pituitary itself, since a male pituitary transplanted under a female hypothalamus will secrete gonadotropin cyclically and can support normal ovarian function. The programming of this behavior lies in the pattern of hypo-



thalamic production of the releasing factors which descend via the hypophyseal portal system and direct the pituitary's synthesis and release of gonadotropins. The cells which produce the releasing factors are neural cells, and any factor which influences gonadotropin release is actually controlling neural tissue. Such an influence has been shown for testosterone. If neonate female rats are exposed to testosterone, on maturation they produce gonadotropin in the acyclic pattern of the male. That is, exposure to androgen at a critical period of development overcomes the brain's genetic femaleness and imprints the male type of hypothalamic-hypophyseal behavior.

In view of this influence of male hormone on nervous function, it was perhaps not surprising to find that testosterone also influences sexual activity. Normal female rats manifest sexual activity patterns which parallel estrus cycling. Administration of testosterone to newborn female rats abolishes the sexual receptivity they would otherwise manifest with sexual maturation, and female hormone therapy of even pharmacologic levels will not overcome this effect. Similarly, castration of the male results in low acyclic levels of random sexual activity. Transplantation of an ovary to such a male, however, is followed by cyclic, gonadotropin-dependent ovarian function and corresponding cyclic sexual receptivity typical of the normal adult female.

In view of these evidences of hormonal influence on sexual behavior, a question that naturally arises is whether differences in non-sexual behavior could be produced by endocrine factors. Elsewhere in this issue Levine presents new data bearing on this point. In response to electric shock stimulation, normal adult male rats show significantly more fighting behavior than females. If the testes are removed in the weaning period, this response is reduced but can be restored by testosterone administration. If castration is performed in the neonatal period, this aggressive behavior is almost eliminated and cannot be restored by any dose of testosterone. Equally, testosterone administration does not produce male-type fighting behavior in females.

It seems, then, that at the level of the brain no less than in genital differentiation, maleness is not directly genetically determined but is the result of imprinting by male hormone.

What are the implications of these studies for man? Several disorders of human sexual develop-

ment indicate that testosterone plays the same positive role in sexual differentiation that it does in other mammals. In testicular feminization, a disorder in which testosterone is physiologically inactive, the patient is a genetic male but the general phenotype is female. In congenital adrenal hyperplasia, genetic females produce excessive androgen and many male features develop. How much of a role does the hormone play in man's neural development? Is it possible that hormonal defects underlie some of the behavioral disorders such as transsexualism?<sup>2</sup> Without entering the lists on whether homosexuality is a disease, it is clear that affected persons are often troubled and doctors are entitled to ask whether understanding of a hormonal factor in pathogenesis could lead to some new form of assistance. Finally, in the face of a growing insistence on sexual equality, what constraints are imposed on this social evolution by the fact that half the central nervous systems of our race develop bathed in testosterone? One must hope that the answers to such questions will emerge from studies such as Levine's, and in light of the current pace of social change, the development of this field has come none too soon.

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## The Clinician in Medical Investigation— The Carcinoid Spectrum As an Example

MR. COHEN'S SCHOLARLY REVIEW of the carcinoid spectrum, printed elsewhere in this issue, has indirectly raised several points which it is well to emphasize because of their obvious implications

for the practicing physician. The study of the pathogenesis of the carcinoid syndrome has encompassed only 16 years. The initial investigation was stimulated by critical observations made by men who were predominantly clinicians. Only after the signs of simple uncomplicated pulmonary stenosis were shown to be incompatible (in appearance and in timing) with the signs of a carcinoid tumor was a careful analysis of the causative factors in the syndrome initiated. Had clinicians remained silent, investigation might have been delayed although methods for effective study were available.

Definition of a worthwhile clinical problem rests on critical analysis of data related to a disease state. The challenge of detection can be most effectively met by the practitioner. The more sensitive we are to "unusual" signs and symptoms that do not "fit with" a defined disease, the more likely we are to stimulate research which leads to important biologic discovery. As exemplified by the investigations of the carcinoid syndrome, such discovery often has wide application that can feed back and raise the standards of diagnosis and therapeutics. Thus investigations of the carcinoid syndrome have led to unanticipated rewards in understanding the pathogenesis of such entities as rheumatoid arthritis, endotoxemia and the biochemical mechanisms which produce physiologic circulatory adaptation in the neonate.

The article in this issue has drawn attention to the dangers of complacency about a disease. Some confidence is justified as we learn more about pathogenetic factors, thereby allowing accurate diagnosis and efficacious therapeutic regimens. However, unless we routinely review and analyze our knowledge and use the information supplied by patients, progress stops and suboptimal therapy results. Thorson, Sjoerdsma, Oates, Lembeck, Sandler and others have demonstrated that when symptoms are carefully analyzed they often (1) reveal subtleties that require investigation, leading to the discovery of new pathogenetic factors; (2) allow objective means not only for making a diagnosis but also for easily recognizing the primary site of a tumor; (3) lead to more specific and effective palliative therapy; and (4) allow estimation of prognosis and determination of an optimal and economical plan for management of the patient. If we assume omniscience about a disease, then we can

expect, among other obvious disadvantages, inaccurate diagnosis which can lead to ineffective and unnecessarily dangerous therapy; unfortunate delays in development of practical clinical and basic information; underutilization of publicly sponsored and personal resources; and self-recrimination and lack of respect between members of the health team.

Critical thought expressed by the scientific community has led to the discovery of prostaglandins, insulin and a variety of hormonal peptides produced by the carcinoid tumor. Such investigations have allowed us (1) to explain and treat symptoms that could not have been caused by serotonin or its metabolites; (2) to use objective measurements to diagnose a variable feature of the disease in any patient rather than being satisfied with shot-gun therapy; and (3) to design studies that form the basis for progress in biochemical, physiologic, pharmacologic and clinical research. Indeed Mr. Cohen (a fourth year medical student) has been able to deduce from his extensive reading that another facet of the biochemistry of the carcinoid tumor must be explored. He is correct in assuming that the niacin deficiency syndrome is not likely to be explained by simple shunts of tryptophane to the synthesis of serotonin. Current investigation indicates that a number of previously undiscovered indole acids (and presumably their precursor amines) may be formed by patients with the carcinoid spectrum, that the quantity of indole excretion may lead to diagnosis of the disease in patients with normal excretion of 5-hydroxyindoleacetic acid (5 HIAA) and that the pattern of excretion may provide a simple biochemical means to establish the site of the primary tumor and to explain the pathogenesis of some newly appreciated symptoms. Continued objective thought about this spectrum (and all disease) is clearly a worthwhile endeavor for the physician. The importance of continued investigation based on leads from the critical student and practitioner of medicine is illustrated by the story of the carcinoid syndrome, but is by no means limited to this rare problem.

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## Community Mental Health Services

WITH THE ENACTMENT of the Community Mental Health Centers Act (Public Law 88-164, 1964; Public Law 89-105, HR 2985, 1965; Public Law 89-105, 1966), the mental health groups in this country have been given a mandate to provide comprehensive mental health services for the prevention and treatment of mental illness and rehabilitation of the mentally ill. Now more than 200 of these centers are in operation.<sup>1</sup> They provide a model, in many ways, of a comprehensive health center. The mental health field may well lead the way in demonstrating the feasibility of this approach for the delivery of more efficient and higher quality medical services to a defined population.

California has been in the forefront of the development of state legislation in the community mental health field. It was the second state in the country to enact such legislation, in 1957, following New York in 1954. California legislators such as Senator Alan Short, former Assemblyman Donald B. Doyle, and Senators Frank Lanterman and Nicholas Petris are to be commended for their efforts on behalf of the mentally ill. State support for the community mental health program has risen from an original appropriation of \$786,000 for support of 12 programs to \$72,436,000 for the 1970-1971 fiscal year, supporting 58 programs.

The original Short-Doyle Act of 1957 was revised in 1969, at which time the Lanterman-Petris-Short Act was also passed, and this, too, has been amended in response to requests from professionals and interested citizens. The new Short-Doyle Act named the county as the local unit of government to establish a mental health program, made community mental health centers mandatory in counties with populations of 100,000 or more, set the state-county reimbursement formula at 90 percent, 10 percent, and established the principle of a single coordinated

system of care for the mentally ill. Ten services were named: inpatient; outpatient; consultation, education, and information; emergency; research and evaluation; diagnostic; partial hospitalization; rehabilitative; pre- and after-care; and training. The Lanterman-Petris-Short Act emphasized the right to judicial review when individuals are held involuntarily, specified legal and civil rights guaranteed to all patients, and established conservatorship procedures for patients who are declared gravely disabled as a result of mental disorder or impairment by chronic alcoholism.<sup>2</sup>

The report by Karno and Knipe in this issue of CALIFORNIA MEDICINE on "Contracting for the Delivery of Public Mental Health Services" stresses the importance of state community mental health legislative provisions that permit a county to contract with private agencies for the delivery of mental health services. This is an excellent example of cooperative and constructive efforts by the public and private sectors toward a common goal of providing needed mental health care. It is an example, too, of appropriate utilization of available resources in the community. The authors point out the benefits and the problems of such contractual arrangements, which provide financial support to private agencies with an opportunity to expand well functioning existing and unique programs without the delay inherent in setting up new public programs. This is especially necessary where such agencies serve populations where a great need exists.

There are difficulties, of course, in setting up such public-private contracts. Some agencies are very selective about the types of patients they will serve; the authors mention in particular those that provide only "intensive and extensive psychoanalytically focused treatment of a small number of persons." Salaries for professional personnel may be higher in private than in public agencies, producing unfair competition for scarce manpower within the same funding system. Some agencies resent regulations and standards imposed by a contract with a public agency, in particular resisting evaluative procedures that admittedly are difficult to establish on an objective basis. All in all, however, the authors believe that the advantages outweigh the disadvantages in these contractual arrangements between public and private agencies.

Spensley and his co-authors, also writing in



this issue on "LPS and the Mental Health Center," provide impressive data showing that the principles inherent in the Lanterman-Petris-Short legislation led to marked reductions in admissions to state mental hospitals and to reductions in the duration of stay in hospital. (They wisely point out, however, that systematic, long-term evaluation of such a shift in therapeutic orientation is yet to be carried out.) Concomitantly, the use of outpatient services increased, although whether by patients in after-care, by types of patients formerly hospitalized, or by tapping a pool of patients not seen before is not clarified. Involuntary inpatient admissions decreased decidedly, and the great majority of them were for periods of three days or less.

There is no unanimity among psychiatrists that the community mental health movement is necessarily the best approach to meeting the need for better delivery of mental health services. It has been described as "wholesale psychiatry," and serious questions have been raised as to the quality of services provided to individual patients. Some have decried the apparent denigration of the one-to-one doctor-patient relationship and have regarded the community mental health approach as superficial. We do not know, as yet, that the shorter the stay in hospital the better, or that eliminating or reducing the period of hospital treatment will save money in the long run.

Some psychiatrists feel that with short periods in hospital and early discharge to the community, patients do not have sufficient time to work through to the solution of the acute problems that led to their admission, and that, as a result, readmission rates are considerably higher. Moreover, many problems require the resolution of intrafamily and interpersonal tensions, and this takes time. Few studies have evaluated the burden placed on patients' families when patients are kept within the family group despite evidence of overt psychopathologic and behavioral problems.<sup>3,4</sup> It frequently is necessary to make appropriate referral to agencies and physicians for continued treatment, and such plans often require more than a few days to implement.

However, the proponents of short hospital stay insist that hospital treatment should be used only for the rapid resolution of crisis situations and then only when absolutely necessary; other problems can be worked out on an ambulatory basis.<sup>5</sup> If repeated admissions are required, this is still

better than long periods in hospital that may well induce exaggeration of dependency problems and interfere with adequate social rehabilitation. The community mental health concept, according to this view, has as its goal social rehabilitation rather than primarily the resolution of psychodynamic conflicts.

The fact remains that the mental hospital population in the United States has fallen from a little more than 500,000 ten years ago to less than 400,000 now, and in California from 36,853 to 12,671. The rapid development of the community mental health movement throughout the country has played a significant role in this reduction. Psychiatry points with pride to this accomplishment.

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## The 100th Annual Scientific Assembly

IN THIS ISSUE is to be found the program of the 100th Annual Scientific Assembly. This centennial assembly reminds us that even after a hundred years of growth and change a basic purpose of the CMA is still "to promote the science and art of medicine." The program developed by John Dillon and his Committee on Scientific Assemblies reflects the enormous scope of medicine's scientific interest as it exists today. Come to Anaheim. It will be worth it. And you can take in Disneyland too.

# CASE REPORTS

## Arteriographic Demonstration Of a Giant Islet Cell Tumor Of the Pancreas

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ISLET CELL TUMORS of the pancreas are infrequently encountered. Frantz found 24 islet cell tumors in 9,158 autopsies, for an incidence of 0.26 percent.<sup>1</sup> Functional islet cell tumors may be subdivided into three types depending upon the clinical manifestations: (1) Insulinoma, composed predominantly of beta cells and associated with episodic hypoglycemia, which is the most common; (2) a non-beta cell variety associated with the Zollinger-Ellison syndrome; and (3) a tumor characterized by the "F" cell, which is first manifested by severe diarrhea and hypokalemia.<sup>2</sup>

Large, nonfunctioning islet cell tumors, first noticed as abdominal masses or producing symptoms due only to local pressure effects, are even more unusual. Howard's review cited only 14 such cases reported up until 1959.<sup>3</sup> Forshall et al reported the largest known islet cell tumor.<sup>4</sup> The tumor weighed 1,075 grams and was in a 7-year-old patient. Brunschwig reported a functioning adenoma weighing 673 grams.<sup>5</sup> Sandrolini and Polcyn recently reviewed the subject while reporting a nonfunctioning tumor weighing 692 grams.<sup>6</sup>

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We did arteriographic studies on a patient with a 592-gram islet cell adenoma. The arteriographic appearance is virtually diagnostic and such studies are recommended when surgical resection of these vascular tumors is contemplated.

### Report of a Case

A 44-year-old white man had been considered mildly diabetic for years, and had received exogenous insulin for increasing glycosuria for three to four years before the present illness. He had noted increasing anorexia and fatigability in 1967, and also had symptoms suggestive of mid-morning hypoglycemia. The latter were alleviated when insulin dosage was reduced, but fatigue continued and he lost 12 to 15 pounds in the late months of 1967. By December 1967 he began to have epigastric discomfort, and became aware of a large mass in his abdomen. There was no history of ulcer disease or diarrhea.

In January 1968 the patient was referred to the National Cancer Institute. Upon admission his laboratory data, including fasting blood sugar, was within normal limits. A firm, slightly tender, 10 x 7 cm mass was palpated in the left upper quadrant of the abdomen. An upper gastrointestinal series revealed remarkable anterior, lateral and inferior displacement of the stomach.

Selective hepatic artery injection revealed a very large gastroduodenal artery and tumor vascularity from the pancreaticoduodenal arcade, and the dorsal pancreatic artery. There was no hepatic metastasis (Figure 1).

The left gastric artery supplied the tumor via its terminal branches along the lesser curvature of the stomach. The left hepatic artery originated from the left gastric artery (Figure 2). Demonstration of this anomaly later permitted surgical division of the left gastric artery beyond the origin of the left hepatic artery.

Catheterization of the splenic artery revealed remarkable opacification of the tumor mass, with vascular laking and early venous filling. There





Figure 1.—Hepatic artery injection revealing large gastroduodenal artery with tumor vascularity supplied by the dorsal pancreatic and superior pancreaticoduodenal vessels. There are no hepatic metastatic lesions.



Figure 2.—Left gastric artery injection reveals contribution from the anastomotic vessels along the lesser curvature of the stomach. The left hepatic artery arises from the left gastric artery.



Figure 3.—Splenic artery injection with massive tumor vascularity. The large collateral veins fill early because of arteriovenous shunting in the tumor and drain into the superior mesenteric vein as a result of splenic vein obstruction.

were large collateral venous channels via the intestinal veins due to the increased flow as well as to obstruction of the splenic vein (Figure 3).

Superior mesenteric artery injection revealed a small contribution to the tumor from the inferior pancreaticoduodenal arcade.

Surgical exploration through a thoraco-abdominal approach disclosed a large multilobular, extremely vascular tumor involving all of the body and tail of the pancreas. The head of the pancreas was not involved. A thorough abdominal exploration revealed no metastasis. The mass was excised en bloc with the spleen. A tumor capsule was present and was not violated, and the small bowel was not opened or resected. A small amount of normal pancreatic head was left intact, the volume being about 10 percent of the normal pancreas. The final pathologic diagnosis was non-beta islet cell adenoma of the pancreas. Margins of the dissected material were negative for neoplasm. The patient's postoperative course was uneventful.

During the year since the operation, the patient has done extremely well. He is eating an unrestricted diet without pancreatic enzyme supplement, has gained 15 pounds and has no gastrointestinal symptoms. A follow-up celiac and superior mesenteric arteriogram revealed no evidence of recurrence.

## Discussion

Roentgenologic evaluation of the pancreas has recently been reviewed by Rosch<sup>7</sup> and the clinical presentation of pancreatic carcinoma has been correlated with the roentgen findings by Rastogi.<sup>8</sup> Pancreatic arteriography has been reviewed critically by Nebesar and Pollard<sup>9</sup> and Eaton.<sup>10</sup> Arteriographic demonstration of small beta cell tumors has been reported by numerous investigators.<sup>11,12,13,14</sup> However, Bookstein suggested that these tumors can be localized by this technique only 20 percent of the time.<sup>15</sup> Clemett<sup>16</sup> and Zboralske<sup>17</sup> have demonstrated non-beta cell adenomas associated with the Zollinger-Ellison syndrome and advocated wider use of the procedure. McGavran et al used arteriography in the evaluation of a glucagon-secreting alpha cell carcinoma.<sup>18</sup>

The natural history of these tumors is quite variable, and the diagnosis of benignancy frequently must await an extended postoperative interval of clinical observation without evidence

of recurrent disease. Histologic morphology is frequently misleading in predicting prognosis. In two large reviews cited by Howard with 765 collected cases, 74.9 percent were classified as benign, 12.9 percent as suspicious of malignant change and 12.1 percent frankly metastasizing.<sup>3,19</sup> The tumor in this patient was resected with its capsule and without total pancreatectomy. Warren's criteria for benignancy are satisfied: (1) The morphology and the arrangement of the cells must resemble those of islets; (2) there must be a definite capsule; (3) there should be evidence of compression of the adjacent tissue.<sup>20</sup> One year follow-up, including repeat celiac arteriography, revealed no evidence of recurrence.

The clinical history in the present case suggested long-standing diabetes, which was never evaluated beyond periodic determination of glycosuria. During the months immediately preceding his admission to the National Cancer Institute, his exogenous insulin requirements apparently decreased to the extent that he began to experience hypoglycemic attacks on what had previously been a satisfactory therapeutic dose of insulin. Since operation he has required no insulin, has had no glycosuria, and after one year has a normal glucose tolerance curve. A detailed account of the metabolic and histochemical aspects of this case will be the subject of a future report.

The differential diagnosis of a very large vascular mass in the region of the pancreas must include the rare giant islet tumor. Cystadenomas and cystadenocarcinomas are moderately vascular tumors, but are characterized by their multicystic appearance reflected in large avascular areas.<sup>21</sup> Retroperitoneal angiosarcoma and hemangiopericytomas have been described but to our knowledge have not been evaluated arteriographically.

The resection of large, extremely vascular tumors is facilitated considerably by an accurate preoperative demonstration of the arterial and venous communications in the tumor bed. Distortion of the normal vascular anatomy, as well as anomalous origins of major vessels may be documented. In this case, an anomalous left hepatic artery was taken into consideration in planning the surgical procedure.

## Summary

The arteriographic demonstration of a giant islet cell tumor is presented. The extremely vascular nature of the tumor is considered diagnostic.

Knowledge of the vascular architecture is of considerable value at the time of surgery.

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# Angiographic Diagnosis of Polyarteritis Nodosa

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POLYARTERITIS NODOSA, which was first described in 1852 by Von Rokitsky, is a progressive recurrent necrotizing inflammatory panarteritis, involving the medium-sized muscular arteries. It is characterized by visible nodules along these vessels.<sup>1,2</sup>

The incidence of the disease has been reported in other articles.<sup>3-4</sup> Various types of arteritides and suggested causes have been described.<sup>1,2,5,6</sup> Nuzum prefers the term *polyarteritis nodosa* to *periarteritis nodosa*, implying true arterial disease rather than adventitial disease.

Polyarteritis nodosa often presents as a puzzling picture of fever, weight loss, and debilitation. Approximately 50 percent of the patients have hypertension. The variability of presenting signs is well documented.<sup>1,2,3,7,8,9</sup> The development of hypertension is associated with the healing phase and is a sign of a poor prognosis.<sup>5,10</sup> The laboratory is generally of little help.<sup>3</sup>

The frequency of organ involvement is given as follows:<sup>1,7</sup> kidney, 85 percent; heart, 76 percent; liver, 66 percent; gastrointestinal tract, 51 percent; skeletal muscle, 39 percent; pancreas, 35 percent; spleen, 34 percent; peripheral nerves, 27 percent; mesenteric arteries, 25 percent; skin, 20 percent. The probability of a positive skin or muscle biopsy leading to the correct diagnosis, then, is not high and a negative biopsy does not rule out the diagnosis. The difficulty of obtaining a useful biopsy specimen has been described.<sup>11,12</sup>

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Maxeiner, et al give an excellent discussion of this problem.<sup>13</sup>

The renal biopsy has a greater chance of being positive but obtaining the specimen is hazardous. Perirenal hemorrhage may occur and be fatal. An arterovenous fistula has also been described.<sup>9,14</sup>

## Report of a Case

A 45-year-old woman was admitted to hospital September 20, 1968. She had been in good health until the summer of 1966 when she noted pains in her heels. This was followed by morning stiffness of her hands. X-rays were persistently negative, indomethacin, MSD (Indocin®), and aspirin, aluminum glycinate and magnesium carbonate (Bufferin®) were prescribed but gave no relief. A latex fixation test was positive and she was thought to have rheumatoid arthritis. She was subsequently well controlled with varying amounts of Bufferin alone.

In September of 1968, the patient experienced increasing pain in all of her joints with some swelling of her feet. The pains were worse at night and not aggravated by exertion. She complained most of pain in heels, feet, ankles, and knees. No warmth, swelling, or tenderness of the joints was evident.

Ten days before admission, the patient noted the onset of malaise and fatigue with fever up to 102° in the afternoon and back to normal by morning. Sore throat and lymphadenopathy developed, for which erythrocycin was prescribed. Because of the lack of improvement, the persistence of the fever, and the lymphadenopathy, she was admitted for observation and evaluation. Subsequently, costochondral pain and photophobia developed.

On physical examination the patient appeared acutely ill. There were tender enlarged anterior and posterior cervical, axillary and inguinal nodes. Fusiform swelling of the proximal interphalangeal joints with minimal tenderness was noted. The remainder of the examination was within normal limits.

An intravenous pyelogram taken eight years before apparently had been normal. The initial impression was systemic lupus erythematosus. However, the LE preparation was only weakly reactive. Steroids were administered and further laboratory tests were done. Alpha and gamma globulin were above normal. There was 2 plus proteinuria, with many erythrocytes and pig-



**Figure 1.** Selective left renal arteriogram showing the multiple small aneurysms.

mented casts in the urine, along with renal tubular cells and bacteria.

A renal biopsy was performed September 29 and was well tolerated. The microscopic diagnosis was "medullary necrosis, kidney (angiitis?)." Renal biopsy was repeated three days later and the report was "glomerulitis."

Increasing oliguria developed and the patient was placed on fluid restriction. Anti-nuclear fraction was positive undiluted but the results of serology were atypical for systemic lupus erythematosus and the patient was felt to have polyarteritis nodosa or hypersensitivity angiitis. Because of the anuria, the patient was started on a program of dialysis.

On October 6, 1968, an emergency percutaneous transfemoral selective left renal arteriogram was performed (Figure 1) to rule out a renal arteriovenous fistula as a cause of the high output failure.

The patient did not do well, pulmonary edema, hemoptysis and coma developing. She died December 10, 1968.

Autopsy revealed cardiac hypertrophy, disseminated angiitis, nephritis, congestive heart failure, and pericarditis. The angiitis involved the small bowel and kidneys. In the small bowel mesentery were numerous fleshy masses averaging 1 cm in diameter. On cut surfaces, each nodule consisted of a small dilated thickened vessel. Similar nodules were found in the kidneys. In addition diffuse atherosclerosis of the cerebral vessels was noted. No involvement of the hepatic vasculature was found.

## Discussion

Because of the inherent danger in the renal biopsy and the possible futility of the skin or muscle biopsy, x-ray examination has been extensively utilized. The chest x-ray may be normal or show incidental pneumonia. Pulmonary edema may follow renal failure. Characteristic changes are fleeting interstitial pneumonitis and pleural effusion, multiple tiny nodules due to vascular lesions, single or scattered larger nodules due to granuloma or infarct, prominent hilar vessels possibly secondary to pulmonary hypertension, and non-specific cardiac enlargement. Rarely the granulomatous nodules may cavitate. Variable signs in the abdomen secondary to infarcts, hemorrhages, ulceration, or perforation of the gastrointestinal track, or peritonitis may be noted. There may be a mild adynamic ileus or areas of narrowing due to a vascular colitis on the plain film or the barium study. An extensive periostitis may be noted.<sup>8</sup>

Perirenal hemorrhage may be the presenting symptom or occur after excision of a renal biopsy specimen. The appearance and differential diagnosis of this entity have been well described.<sup>3,5,8,15</sup> The intravenous pyelogram may also show abnormalities of the proximal one-third of the ureter.<sup>16,17</sup>

A renal arteriogram is often performed for assessment of hypertension. Selective studies are preferred.<sup>18</sup>

The characteristic arteriographic appearance of polyarteritis nodosa is multiple small aneurysms that are uniform in size, measuring 1 to 5 mm, and associated with medium and small arteries exclusively. Persistent opacification of these aneurysms is seen in the nephrogram phase. Also noted is scalloping of the renal outline and defects in the nephrogram suggesting infarction and loss of cortical substance. The findings are diagnostic.<sup>3</sup> In the healing stage, angiography may not reveal any aneurysms.<sup>19</sup> There is, however, shortening and



decrease of the peripheral arteries and an irregular nephrogram. It is important to remember that the degree of aneurysm formation will vary from case to case and from organ to organ within a particular case.<sup>12</sup>

Multiple aneurysms may also be seen in patients with neurofibromatosis<sup>20</sup> or they may be congenital. In both of these conditions aneurysms occur on the main renal arteries and are extraparenchymal.<sup>3</sup> Mycotic aneurysms have different clinical and bacteriologic findings.<sup>21</sup> Therefore, an aneurysm of the main renal artery only is most likely of congenital or atherosclerotic etiology. Congenital aneurysms occur usually at bifurcations, are frequently multiple and do not involve the intraparenchymal arteries.

### Summary

A case report of a patient with polyarteritis nodosa is presented. The dangers of renal biopsy and the uncertainty of muscle biopsy are emphasized. Selective renal arteriography will show the characteristic and diagnostic aneurysms of the parenchymal small and medium sized muscular arteries.

### TRADE AND GENERIC NAMES OF DRUGS

<i>Indocin</i> ®	..... indomethacin, MSD
<i>Bufferin</i> ®	..... aspirin, aluminum glycinate and magnesium carbonate

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# LETTERS *to the Editor*

## Chemicals in the Environment

IN HIS ESSAY that discussed the impact of synthetic chemicals in the environment (*CALIFORNIA MEDICINE*, November, 1970), Professor Rudd\*\* pointed out that these pollutants might be considered as waste products of our present technology. They do not, however, obey the fundamental ecological law that requires the waste products of a community of organisms to be broken down into primary materials that can be used again and again. Professor Rudd further stated that the "major goals of the socially responsible environmentalist" were to understand the effects upon ecosystems of these pollutants and "to control and to regulate" their input into the global environment. The problems that must be solved and the measures that must be adopted to achieve these goals and to establish a "working control system" are so formidable, however, that Professor Rudd might perhaps be excused for choosing not to comment upon them.

In California the polychlorinated biphenyls were only recently found to be widespread and abundant environmental pollutants. It might therefore be asked how many other persistent pollutants remain undetected by the methods that measure chlorinated hydrocarbons and the heavy metals. Three groups of pollutants were mentioned by Professor Rudd—the organochlorines, the organomercurials, and lead compounds, but as yet we have a very imperfect knowledge of

their distribution in the California environment. We know even less about their effects upon many species now undergoing rapid population changes and we can not predict future rates of accumulation.

The trend in the recent history of science has been toward increased specialization. Yet the answer to the question why the brown pelicans of Anacapa Island are showing abnormal behavior patterns requires expertise in several very different specialties, including ethology, endocrinology, physiology, biochemistry, and perhaps the most important of all, natural history. Determination of the distribution, movements, and effects of the mercury compounds in our coastal waters will require a knowledge of specialties within the broader disciplines of analytical chemistry, microbiology, oceanography and marine biology, in addition to a knowledge of the industrial and agricultural uses of these compounds that constitute the sources of mercury pollution. None of our universities, however, has so far developed a curriculum that will provide the rigorous training that would permit students to use a multi-disciplinary approach in solving the problems of pollution ecology. The training of students is, however, a critical need.

A frequent approach to environmental problems, especially those receiving publicity by the news media, consists of the appropriation of considerable sums of money and the establishment of governmental laboratories and institutes. The procedure is inevitably bureaucratic, slow, and frequently inefficient. Facilities are not open to students and they play no role in the educational process. Instead of communication to the scientific community, interdepartmental memoranda are circulated. Many kinds of research projects,

\*\*Rudd RL: Chemicals in the environment. *Calif Med* 113:27-32, Nov 1970



particularly the long-term studies are best accomplished by such governmental institutions, yet experimental projects are more efficiently accomplished at the universities. Research funds would thereby support students and contribute to the educational function. The current trend toward increasing governmental research activities at the expense of university sponsored research will clearly be disastrous in the long run.

Professor Rudd pointed out that pollutants cross international boundaries. Control will therefore inevitably become an international problem. The developing countries are prone to consider anti-pollution activities on an international level as a scheme for discouraging their own development, which for economic reasons will inevitably follow the same pathways and techniques that have produced pollution in Japan, North America and Europe. In December of 1970, the Food and Agricultural Organization of the United Nations will hold a meeting in Rome to discuss pollution of the sea and the methods that must be adopted to combat it. The papers produced by this conference will be used in turn to prepare for a larger United Nations conference on pollution to be held in Sweden in 1972. The scientists and diplomats participating in these conferences face therefore the responsibility of preparing the framework that will be used for international efforts to regulate and control the input of persistent pollutants into the global environment. It is a formidable challenge, and if these conferences are successful, a technology may yet emerge that will permit man to live in harmony with his environment.

ROBERT W. RISEBROUGH, PH.D.  
*Associate Specialist, Institute  
of Marine Resources,  
University of California, Berkeley*

## Do Not Smoke in Front of Your Dog

*To the Editor:* The sixth anniversary of the Surgeon General's report on cigarette smoking is being observed the week of January 10th by "National Smoking Education Week." The social climate has changed: It has to be a sunny day in January for anyone now to speak favorably about smoking. In fact smoking is rapidly becoming an antisocial act. The captive nonsmoker has begun

to assert his rights to clean air. It is no longer enough to taste the fruits of nonsmoking. Ecologically and morally it is fitting now to agitate against the befouling of enclosed spaces. The inhalation of another's cigarette smoke has been shown to decrease the body's resistance to respiratory disease. Children especially show greater vulnerability to infection when they are enveloped by persistent smoke.

The Auerbach Experiments which demonstrate the carcinogenic properties of cigarette smoke in dogs have led some wags to suggest "be kind to your dog" campaigns. Many inveterate smokers who cannot stop smoking out of respect for their own bodies might be able to do it for their dog's sake. Bumper strips could proclaim "Your Smoking May Be Harmful to Your Dog." The new California Teacher's Health Guide has now officially changed its stand to: Cigarette Smoke *IS* Dangerous to Health. It is time for further thinking on the whole matter.

GERALD HILL, MD  
*San Rafael*

## A New Ethic for Medicine and Society

*To the Editor:* Your editorial of September 1970, "A New Ethic for Medicine and Society," is absolutely incredible. If the matter were not so serious, I would be tempted to think that you meant the editorial to be hideous irony or a twisted joke. A better title would have been "A Non-Ethic for Medicine and Society."

Since you lightly toss about the label, "Judeo-Christian," I certainly feel justified in attaching the label, "Neo-Nazism," to your crude and cruel interpretation of the quality of life and your insensitive machinations for its application. How can you dare to peddle such trash in a country based on the principle that "man has been endowed by the creator with certain inalienable rights, among which are the rights to life, liberty, and the pursuit of happiness?" This is not, and must not become, a country in which the right to life is determined by monstrous egoists who, far from being atheists, want to set themselves up as gods. Moreover, in your biologically oriented so-

ciety, you would reduce man from a state "little less than that of the angels" to one little better than that of animals.

Words harsh enough to describe your editorial do not exist in the English language. That editorial is an abdication not only of medical responsibility but of human decency as well.

REVEREND CHARLES E. MILLER, C.M.  
*Professor of Biology  
St. John's Seminary  
Camarillo*

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*To the Editor:* Heartiest congratulations on the recent editorial in CALIFORNIA MEDICINE, September 1970 on "A New Ethic for Medicine and Society." May all physicians read it and hopefully organize their own study groups on a community level to engage themselves in serious debate concerning these issues.

I have been engaged in weekly discussions for over two years in a large multi-discipline group and our two theologians took offense at the hint of an erosion of the Judeo-Christian ethic and that human lives in the future may be judged by relative rather than absolute values. The many physician members of the group have persuaded them, I believe, that this editorial was sagacious, timely and most inspiring. Our dialogue has been most enriching and mutually educative.

Thanks for continually making CALIFORNIA MEDICINE currently aware.

H. HARRISON SADLER, M.D.  
*Associate Clinical Professor of Psychiatry,  
and Ambulatory and Community Medicine;  
Chief, Psychiatric Liaison Service,  
University of California, San Francisco*

## Where's the Action?

*To the Editor:* Perhaps you or some of our older colleagues can set my thinking straight on some troubling issues? I seek this guidance for I find

myself right in the generation gap—too young to be Establishment and too old to believe in revolution and destruction of institutions.

A concerned group of whoever poses a legitimate problem—say, any number of documented dissatisfactions with health care delivery. Dedicated sincere colleagues of ours who sit in responsible positions acknowledge the legitimacy of these disputations and set about to do something. Why is it that that "something" is invariably referral to committee for "study" or its analogues, the survey, the feasibility study, or the hand-wringing quest for more research. Can nobody do anything about *anything*?

I hate to be facetious but someone told of a "right-on" poster wherein a pleading child in the last stages of malnutrition is saying, "I'm hungry—thank you for calling a Conference on Hunger." Is this the way of the world? Is this necessarily the way of California medicine?

I would hope someone can relieve me of my negative feelings toward committees, councils, societies, and associations. Has anything been done, created or instituted by a committee that has been accepted as effective by the supposed target population?

ALAN D. MATZGER, M.D.  
*San Francisco*

• Who has some answers?—Editor.

*To the Editor:*

## Orthopedic Ecology

The infused young orthopedic surgeon is well versed in re fusing backs.

The confused middle-aged orthopedic surgeon is well versed in re-fusing backs.

The defused old orthopedic surgeon is well versed in refusing backs.

Ergo, the land is profuse with refuse.

CHRISTOPHER A. MASON, M.D.  
*Los Angeles*



# A Critical Comment

EDITOR'S NOTE: *In view of the time which has elapsed since the editorial, "A New Ethic for Medicine and Society," appeared in CALIFORNIA MEDICINE (September, 1970) and because of Dr. Ford's deeply felt concern with this editorial as he has interpreted it, we take the unusual step of reprinting the editorial side by side with Dr. Ford's critical comment and will let the reader judge for himself.*

—M.S.M.W.

Malcolm S. M. Watts, M.D.  
California Medicine

Dear Dr. Watts:

In your letter of 10/20/70, you rejected for publication (because of its length of some 4000 odd words) my critical analysis of your September editorial, "A New Ethic for Medicine and Society"; and asked me to send a shorter version in the form of a "Letter to the Editor," which I am herewith attempting to do. You also implied in your letter that, in my original lengthy article, I had somehow misunderstood or misconstrued your "intent" which was merely to bring what you believe to be "the import of what is already occurring to the readers";—rather than to urge the endorsement and application of the "new ethic" which you were describing;—as I had implied. Therefore, I would like to again summarize my interpretation, by means of paraphrasing some of your own statements; so that the readers may compare my analysis, and then may judge the "intent" of your editorial for themselves. (This will afford you an opportunity, following my remarks, to point out where I have misinterpreted you):

First of all, it seems quite clear to me that your September editorial is advising all of us, your colleagues, to "prepare to apply (this new ethic)," which will "place relative rather than absolute values on such things as human lives," which will "of necessity" destroy the traditional reverence of Western medicine for each and every life. You further suggest that abortion, which you admit is "killing" and "the taking of human life," is a "prototype of what is to occur" under this "new ethic"; and that the physician's role in birth control and birth selection will be extended "inevitably to death selection and death control" (which, I assume, is a euphemistic term for euthanasia). Continuing in the same vein, you intimate that "the new ethic . . . will ultimately prevail"; that the medical profession, which you imply would act somewhat as a rather exclusive and elite committee, will be "deeply involved" and will be "essential in planning and decision-making at many levels" in applying this "new ethic"; and that in the "biologically oriented world society" of the future, the physician's responsibility for placing relative value (and in cases of death selection: apparently, no value!) on human life, might be on a "compulsory basis."

It is apparent, moreover, that you tacitly approve the use of the "very considerable semantic gymnastics" and the "subterfuge" (as you yourself referred to it), being used to rationalize abortion as something other than the

"taking of human life," as one means of increasing "this shift in public attitude" toward the acceptance of "this new ethic." Furthermore, you are quite obviously encouraging our entire profession to apply this new ethic now, without any apparent misgivings or qualification at all, even though you yourself admit that this "carries quite serious philosophical, social, economic and political implications for Western society and perhaps for world society;

(Continued on next page, left hand column)

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## (The Editorial)

### A New Ethic for Medicine and Society

THE TRADITIONAL Western ethic has always placed great emphasis on the intrinsic worth and equal value of every human life regardless of its stage or condition. This ethic has had the blessing of the Judeo-Christian heritage and has been the basis for most of our laws and much of our social policy. The reverence for each and every human life has also been a keystone of Western medicine and is the ethic which has caused physicians to try to preserve, protect, repair, prolong and enhance every human life which comes under their surveillance. This traditional ethic is still clearly dominant, but there is much to suggest that it is being eroded at its core and may eventually even be abandoned. This of course will produce profound changes in Western medicine and in Western society.

There are certain new facts and social realities which are becoming recognized, are widely discussed in Western society and seem certain to undermine and transform this traditional ethic. They have come into being and into focus as the social by-products of unprecedented technologic progress and achievement. Of particular importance are, first, the demographic data of human population expansion which tends to proceed uncontrolled and at a geometric rate of progression; second, an ever growing ecological disparity between the numbers of people and the resources available to support these numbers in the manner to which they are or would like to become accustomed; and third, and perhaps most important, a quite new social emphasis on something which is beginning to be called the quality of life, a something which becomes possible for the first time in human history because of scientific and technologic development. These are now being seen by a growing segment of the public as realities which are within the power of humans to control and there is quite evidently an increasing determination to do this.

What is not yet so clearly perceived is that in order to bring this about hard choices will have to

(Continued on next page, right hand column)

(Dr. Ford's letter, continued)

... (that it) will of necessity violate and ultimately destroy the traditional Western ethic with all that this portends; ... and that this of course will produce profound changes in Western medicine and Western society."

Now, as I indicated in a previous letter to you; it seems hard to believe, after advising your fellow-physicians to apply a "new ethic" which would entail the taking of human life, possibly on a *compulsory* basis, and which would of necessity destroy the traditional Western ethic in the "biologically oriented world society" (Brave New World?) of tomorrow, that you could really ask me to take seriously your statement that "one of the principle reasons I decided to write (that) editorial was my concern with what I perceive to be the erosion of the (traditional?) ethic to which I believe we both adhere, . . ." as you expressed it to me in your personal letter (10-20-70). Is not the contradiction in attitudes expressed in your letter to me on the one hand, and in your September editorial on the other, sort of "schizophrenic";—as you yourself put it?

And a few other questions come to mind: Isn't it contradictory to ask physicians to "prepare to apply (this new ethic)"; in which the physician would be seen, at one moment eagerly easing suffering and prolonging life out of a passionate concern for humanity in the form of sick and suffering individuals, and at the next moment wantonly killing or deliberately neglecting human individuals because he cares passionately for humanity *collectively* and wants to save it from some ill-defined calamity called an ecological crisis? And doesn't such a situation present some sort of conflict of interest for the physician, to say the least?

One is compelled to ask further at this point: Which is it to be, more of us or less of us? (Paul Ehrlich has said that the "population explosion" is essentially a numbers game!) So, if it really must be *less of us*, then I think the only logical and sensible thing for us physicians to do is to go out of business in favor of the mortician or the hangman, or both;—in order to help decrease our numbers!

And isn't it true that you were, in essence, in your editorial, inviting physicians to play "God" with the human lives entrusted to their care? But if our government is bound constitutionally to recognize each individual's inalienable right to life, which it does not dare violate without "due process" of law; should the medical profession consider itself a special elite, above the government and above the law? Have we rejected the "divine right" of kings in former centuries only to adopt the "divine right" of physicians in our own?

And then, in an era when it has become quite fashionable to begin discovering some rather new, even though ill-grounded, peripheral rights, such as the political right to medical care; does it seem quite fitting or reasonable that we should begin questioning peoples' much more central and inalienable right to life?

And haven't we all held it a truism, as good humanitarians, that "no man is an island, entire of itself"? That being the case: if we have really reached a point in history when the right to life of each and every human is no longer going to remain inviolable, as a matter of public policy; then it follows that, ultimately, none of us is safe! And are we physicians really ready to publicly repudiate the sentiment, which has generally been held as an ideal in our contemporary culture: "... every man's death diminishes me ... for I am involved in mankind"?

In another vein: Considering the fact that one of the themes of the upcoming CMA Convention (just co-inciding)

(Please turn to next page)

(The editorial, continued)

be made with respect to what is to be preserved and strengthened and what is not, and that this will of necessity violate and ultimately destroy the traditional Western ethic with all that this portends. It will become necessary and acceptable to place relative rather than absolute values on such things as human lives, the use of scarce resources and the various elements which are to make up the quality of life or of living which is to be sought. This is quite distinctly at variance with the Judeo-Christian ethic and carries serious philosophical, social, economic and political implications for Western society and perhaps for world society.

The process of eroding the old ethic and substituting the new has already begun. It may be seen most clearly in changing attitudes toward human abortion. In defiance of the long held Western ethic of intrinsic and equal value for every human life regardless of its stage, condition or status, abortion is becoming accepted by society as moral, right and even necessary. It is worth noting that this shift in public attitude has affected the churches, the laws and public policy rather than the reverse. Since the old ethic has not yet been fully displaced it has been necessary to separate the idea of abortion from the idea of killing, which continues to be socially abhorrent. The result has been a curious avoidance of the scientific fact, which everyone really knows, that human life begins at conception and is continuous whether intra- or extra-uterine until death. The very considerable semantic gymnastics which are required to rationalize abortion as anything but taking a human life would be ludicrous if they were not often put forth under socially impeccable auspices. It is suggested that this schizophrenic sort of subterfuge is necessary because while a new ethic is being accepted the old one has not yet been rejected.

It seems safe to predict that the new demographic, ecological and social realities and aspirations are so powerful that the new ethic of relative rather than of absolute and equal values will ultimately prevail as man exercises ever more certain and effective control over his numbers, and uses his always comparatively scarce resources to provide the nutrition, housing, economic support, education and health care in such ways as to achieve his desired quality of life and living. The criteria upon which these relative values are to be based will depend considerably upon whatever concept of the quality of life or living is developed. This may be expected to reflect the extent that quality of life is considered to be a function of personal fulfillment; of individual responsibility for the common welfare; the preservation of the environment, the betterment of the species; and of whether or not, or to what extent, these responsibilities are to be exercised on a compulsory or voluntary basis.

The part which medicine will play as all this develops is not yet entirely clear. That it will be deeply involved is certain. Medicine's role with respect to changing attitudes toward abortion may well be a prototype of what is to occur. Another precedent may be found in the part physicians have played in evaluating who is and who is not to be given costly long-term renal dialysis. Certainly this has required placing relative values on human lives

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(Dr. Ford's letter, continued)

dentially?) is "The Physician as Ecological Activist," might one not justifiably suspect that you could be unfairly using your official position to condition that Convention and its Delegates, by means of a rather one-sided presentation in our official journal, to your own personal ideology? And aren't you being presumptuous in attempting to speak for our entire, CMA membership of some 23,000 diverse physicians on this rather controversial (not to say, revolutionary) subject, with all its far-reaching implications?

And don't you really think that the rest of our society should be consulted for its *informed consent*,—*beforehand*? Shouldn't society, *as a whole*, (and then only after some rather prolonged, in-depth, *public* discussions) have a lot more to say about all this; rather than have its values and its future determined for it by the arbitrary directives of an elite committee of physicians? How do you suppose our citizenry-at-large is eventually going to view the motives and react to the behavior of physicians who, without deferring much to the wishes of the ultimate victims, proceed to push for changes in public policy of such far-reaching consequences as to produce "profound changes in Western society," or who attempt to appoint themselves as a special elite by expanding the social role and the personal power and privilege of the physician?

And isn't your "new ethic," like the "new morality," merely the old "unprincipled expediency" and the old "immorality" dressed up in a new name? And shouldn't you label your advocacy of "this new ethic" for what it really is: —a crass effort to sell unprincipled expediency or utilitarianism or pragmatism as an easy, but oversimplified, "solution" to this alleged overpopulation problem, through the use of such techniques as "rationalization, semantic gymnastics, and subterfuge" (to use your own terms again)? In this context, J. W. Fulbright (surprise to some, I'm sure!) is credited with having said that the idea that the end justifies the means is a totalitarian concept.

But your editorial is just one example, among many, of a danger being engendered by the exaggeration and hysteria of the alleged ecological crisis, which presents an apparently legitimate excuse to those who have just been aching to make what would ordinarily be considered unwarranted attacks on our traditional Western ethic. (And I include in that term all those corny, middle-class values such as marriage, motherhood, children, family, home, etc.)

Now, we all passionately want clean air and clean water, among other things. And nobody wants people to starve. And we would all like these ecological problems solved (or improved as much as possible) as soon as possible, by every possible *ethical*, *moral*, and *humane* means. But let's not start talking about killing people in order to solve their problems, either individually or collectively. Let's be constructive rather than destructive. Let's not throw the baby out with the bath water.

And it might be the beginning of wisdom on this particular subject if we were all to pay some attention to the very open-minded and truly scientific attitude expressed by Chauncey D. Leake (N.Y.J. Med, 1960): "Let us remember always that whatever truth we may get by scientific study about ourselves and our environment is always relative, tentative, subject to change and correction, *and that there are no final answers.*"

Sincerely

JAMES H. FORD, M.D.  
Associate Editor  
LACMA BULLETIN

(The editorial, continued)

and the impact of the physician to this decision process has been considerable. One may anticipate further development of these roles as the problems of birth control and birth selection are extended inevitably to death selection and death control whether by the individual or by society, and further public and professional determinations of when and when not to use scarce resources.

Since the problems which the new demographic, ecologic and social realities pose are fundamentally biological and ecological in nature and pertain to the survival and well-being of human beings, the participation of physicians and of the medical profession will be essential in planning and decision-making at many levels. No other discipline has the knowledge of human nature, human behavior, health and disease, and of what is involved in physical and mental well-being which will be needed. It is not too early for our profession to examine this new ethic, recognize it for what it is and will mean for human society, and prepare to apply it in a rational development for the fulfillment and betterment of mankind in what is almost certain to be a biologically oriented world society.

# LPS and the Mental Health Center

JAMES SPENSLEY, M.D., PAUL H. WERME, M.A., JAMES T. BARTER, M.D.,  
AND DONALD G. LANGSLEY, M.D., *Sacramento*

A NEW LEGISLATIVE ACT dealing directly with delivery of mental health services became effective in California on July 1, 1969. This act, known as the Lanterman-Petris-Short Act (LPS), proposed to accomplish the following:

"(a) To end the inappropriate, indefinite, and involuntary commitment of mentally disordered persons and persons impaired by chronic alcoholism, and to eliminate legal disabilities;

"(b) To provide prompt evaluation and treatment of persons with serious mental disorders or impaired by chronic alcoholism;

"(c) To guarantee and protect public safety;

"(d) To safeguard individual rights through judicial review;

"(e) To provide individualized treatment, supervision, and placement services by a conservatorship program for gravely disabled persons;

"(f) To encourage the full use of all existing agencies, professional personnel and public funds to accomplish these objectives and to prevent duplication of services and unnecessary expenditures."<sup>1</sup>

Examination of several salient factors of inpatient care before and after LPS will help to evaluate some of the results of this legislation. Data reported for Sacramento Medical Center includes all admissions to psychiatric wards. No diagnostic category is excluded. State hospital data excludes mental retardation but no other category.

## State Hospital Admissions

DeWitt State Hospital, located in Auburn, California, has served as the primary state hospital for residents of Sacramento County. During the

period of July through December, 1968, there were 428 admissions to DeWitt from Sacramento County. During the same period of 1969, this figure decreased dramatically (Chart 1). Corresponding with this decrease, there has been an accompanying increase in the average end-of-month outpatient caseload at the Sacramento County Mental Health Services, from 584 in July through December, 1968, to 1,134 in the like period of 1969. This latter increase may be accounted for by both the great expansion that has taken place in the community mental health program in Sacramento since July 1, 1969, and the reduction in the number of Sacramento County patients receiving treatment outside their community of residence.

Direct transfers from Sacramento Medical Center to all California State Hospitals also show a striking change (Chart 2). In the period July through December, 1968, a total of 229 patients were transferred from Sacramento Medical Center to California State Hospitals. During the corresponding period of 1969 the total was 48 patients.

## Legal Status of Patients

Chart 3 presents the data on involuntary inpatient admissions to Sacramento County Mental Health Services for the period July through December 1968 as compared with those in the like period of 1969. During the 1968 period, approximately 60 percent of the total admissions to inpatient services were involuntary. The comparable figure for the 1969 period was 20 percent.

At present, involuntary admissions under LPS involve a brief form which recommends 72-hour involuntary detention for psychiatric evaluation and treatment. The law further provides for additional periods of involuntary detention, de-

<sup>1</sup>From the Sacramento Medical Center Mental Health Services and the Department of Psychiatry, University of California, Davis, School of Medicine.

Submitted, revised, June 18, 1970.

Reprint requests to: 2315 Stockton Boulevard, Sacramento, Ca. 95817 (Dr. J. Spensley).



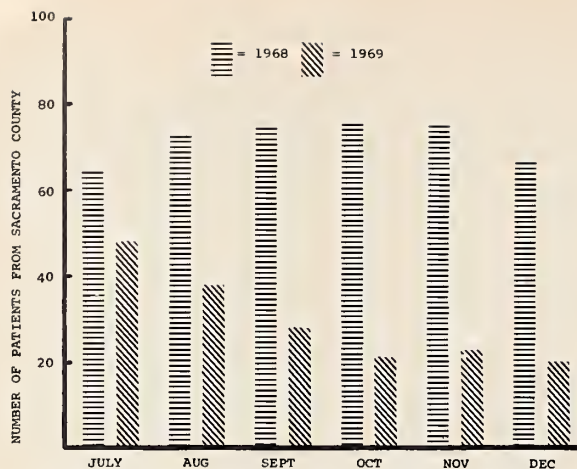


Chart 1.—Number of admissions to DeWitt State Hospital from Sacramento County by months.

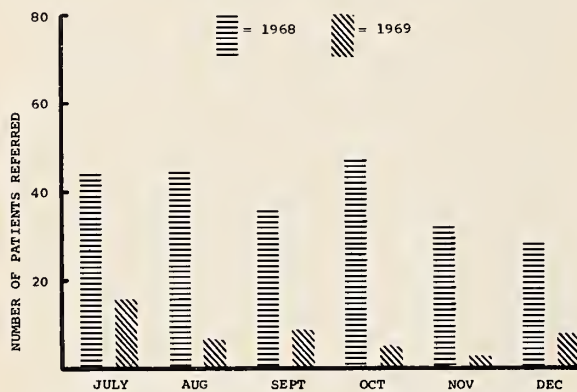


Chart 2.—Number of direct referrals from Sacramento Medical Center to State Hospitals.

pending upon the symptoms observed. An additional 14 days of treatment is available for persons showing serious psychiatric symptoms which "gravely disable" him or make him a danger to himself or others. An additional 14 days may be requested for intensive treatment of patients who are considered to be suicidal. A further 90-day detention may be requested for patients considered to be "imminently dangerous." Other involuntary retention in hospital involves the appointment of a conservator for patients judged to be "gravely disabled." The law also provides for periodic review of the conservatorship.

For the period July through December 1969, the vast majority (80 percent) of inpatients treated at the Sacramento County Mental Health Services involuntarily were on an involuntary

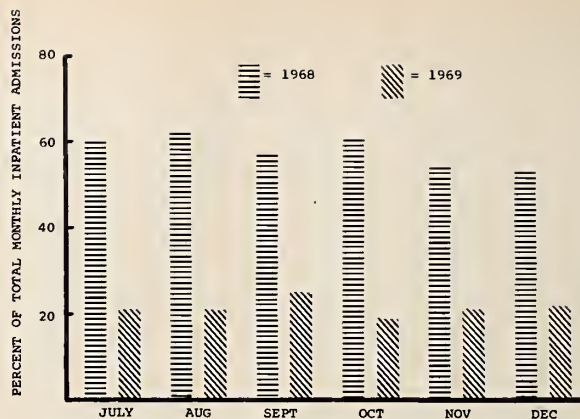


Chart 3.—Percent of total monthly inpatient admissions to Sacramento Medical Center which were involuntary admissions.

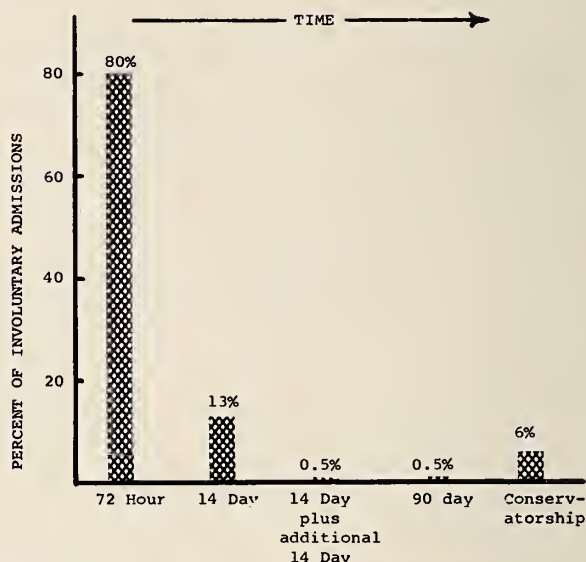


Chart 4.—Percent of a total of 215 involuntary admissions to Sacramento Medical Center resulting in various legal status classifications.

status for no longer than 72 hours (Chart 4). Of the total of 215 involuntary patients admitted during that period, only 42 (20 percent) were detained longer than 72 hours. Twenty-seven of these 42 patients (13 percent of the total number of involuntary patients) were detained for only an additional 14 days beyond the 72 hours. One patient was detained for that 14-day period plus an additional 14 days. One patient was certified beyond this for 90 days, and 13 patients (6 percent of the 215) were placed under conservatorship. The data in Charts 3 and 4 clearly show both a large decrease in the incidence of

involuntary hospitalization and a trend away from long-term involuntary hospitalization.

## Discussion

There is general agreement throughout the psychiatric community that local treatment for mental disorders is more effective and more humane than treatment in a facility located far from the patient's home and family. The Lanterman-Petris-Short legislation, therefore, is in accord with the generally accepted mental health movement within the United States. Despite local treatment, however, it seems from the 1969 experience that there are a few patients for whom prolonged treatment in a hospital is needed. The extent of this need would appear to be significantly less than has been previously believed. This is reflected nationally in a gradual decrease in the populations of state hospitals concurrent with a shift in the care of patients to community facilities. The enthusiastic acceptance of this concept by the Sacramento County Mental Health Services staff has undoubtedly influenced the shift in treatment orientation reported in this

paper. The long-term effects of this shift from state hospital to voluntary treatment in the community will require systematic evaluation.

Experience to date has brought some problems to light. A few patients treated involuntarily for 17 days may remain still too ill to participate voluntarily in treatment, whether as outpatients, inpatients or intermittently in or out of hospital. This is usually characteristic of patients who have paranoid psychosis of a relatively acute nature. This group might better be served if an additional category of involuntary treatment were available.

## AUTHORS' NOTE

Recent analysis of data currently being compiled at Sacramento Medical Center indicates that the trends reported in this paper are continuing in the same direction. For the period January through April, 1970, admission and referral data are now available. With respect to Sacramento County residents admitted to DeWitt State Hospital during this period, the figures are as follows: 34 in January, 22 in February, 25 in March, and 14 in April. In addition, the number of direct referrals to all state hospitals from Sacramento Medical Center continues to decrease: 17 in January, 6 in February, 16 in March, and 5 in April. Conservation requests for January through April 1970 were 32, which represents 6.2 percent of all admissions.

## REFERENCE

1. *California Welfare and Institutions Code*; Division 5, Community Mental Health Services, Part 1. The Lanterman-Petris-Short Act; Chapter 1. General Provisions; Section 5001

## CAUDAL ANESTHESIA IN OBSTETRICS

"Caudal anesthesia in obstetrics, given during the first stage of labor—in the primigravida at 6 to 8 cm and in the multigravida at 4 cm—is associated with a marked increase in operative deliveries, such as posterior arrest requiring manual or forceps rotation. If the caudal should stop labor, stimulation of contractions by oxytocics with its attending risks is required. The other option is to allow the caudal to wear off and permit labor to resume. This entails administration of a second anesthesia with its associated risks. Consequently in our obstetric practice we prefer the terminal caudal. This eliminates unnecessary operative intervention, oxytocic stimulation, and a second anesthesia."

—JAMES V. McNULTY, M.D., Los Angeles

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# Contracting for the Delivery of Public Mental Health Services

MARVIN KARNO, M.D., *La Jolla*, AND  
WILLIAM KNIPE, M.S.W., *Los Angeles*

THE CALIFORNIA SHORT-DOYLE legislation of 1957 provided for cost sharing between the state and local governments for the provision of community mental health services for those who could not afford private care. The Los Angeles County Department of Mental Health came into being in 1960, and in 1962 the first contract had been executed between Los Angeles County and a private mental health service agency. This represented the initiation of a partnership between the state, the county and the private sector for delivering mental health services in Los Angeles County. By 1965 six contracts were in force, supported by a half million dollars annually in state and county funds. They provided for outpatient services to children and adults in widespread areas of the county. These contracts were with agencies that operated at some distance from county facilities or that provided services generally not available in the Mental Health Department's directly operated programs. The requirements for contracting, apart from compliance with Short-Doyle standards and regulations, demanded community involvement and some secure financial base of support in the private agency's community. Specifically, it was required that the contracting agency had been in operation for at least three years before county funding became available. Moreover, a limit was set that no more than 75

percent of the agency's net operating budget could be provided under the contract. A further provision was that county funds could not be used to replace other support funds which would have been available in the absence of the contract. That is, county funds could replace money which no longer would be available under any circumstances; but other funds could not be withdrawn solely because they could now be replaced by county funds.

The California Community Mental Health Services Law, comprising the Lanterman-Petris-Short Act and a revised Short-Doyle Act, became effective on July 1, 1969. Among its many stipulations was the mandate to each county to "... provide for the most appropriate and economical use of all existing public and private agencies and personnel."

This provision of the legislation was interpreted by both the Mental Health Department and private mental health agencies as strong support for and encouragement by the state for the maximum feasible use of the contract mechanism, consistent with community needs, the service capacity of the public sector, sound professional standards and the responsible use of limited tax funds. At present 17 contracts are in force, at an annual expenditure of approximately 1.5 million dollars, and distributed among inpatient services, outpatient services, day care and specialized services such as suicide prevention and a "hot line" program. In addition, discussions or negotiations are in

At the time of writing, Dr. Karno was Chief Deputy Director and Mr. Knipe was Contract Coordinator, Los Angeles County Department of Mental Health.

Reprint requests to: Department of Psychiatry, University of California, San Diego, P.O. Box 109, La Jolla, Ca. 92037 (Dr. M. Karno).

progress with 26 other private agencies concerning the possible contracting for a wide range of mental health services throughout the county. It has become apparent that there are many benefits and many problems inherent in the contract mechanism. These may for convenience be considered as advantages and disadvantages.

#### *Advantages of contracting for mental health services:*

- Since private agencies may have explored on a small scale or in particular localities, innovative programs to meet special needs, contracting with such agencies may allow for greater flexibility, range and variety in the delivery of public services than might otherwise be possible.

- Contracts with already operating agencies provide public services and allow for the development of satellite services in poverty areas without the frustrating time delays involved in the "tooling up" procedures of recruiting staff and developing the physical plant for a new public agency program.

- The contract mechanism allows for the purchase of a known product, in so far as this can be determined by professional and management review, reputation and site visits.

- A contract to provide for public services tends to strengthen the private agency by providing a tax-fund base of support for part of its program.

- A contract to provide for public services tends to broaden the community involvement of the private agency and extends the professional reach of such agencies into populations of greatest need.

- A contract to provide for public services may provide the stimulus to a private agency to serve more severely disordered and low income individuals and families than it might otherwise.

- The contract mechanism allows for some blurring to take place of status distinctions between private and public care.

#### *Disadvantages of contracting for mental health services:*

- The orientation of the private agency may be very difficult to sway away from narrowly selective policies with regard to the population served and the modes of treatment utilized. For example, the intensive and extensive psychoanalytically focused treatment of a small number of persons

selected for particular characteristics is hardly a desideratum today in public mental health policy. Yet such a *modus operandi* still characterizes some prestigious, private mental health agencies in this country. Such agencies, particularly their lay boards of directors, may show considerable cultural lag in operational change even while actively seeking and after obtaining tax monies for providing public care.

- The public health agency usually operates with civil service requirements and politically sensitive staff salary and professional benefits limitations which may be bypassed by the private agency. Thus, the contract for service may produce direct and unequal competition for scarce personnel within the same funding system.

- A great deal of time and effort is required for the degree of administration and supervision of contracts that is essential to provide the accountability necessary for a public agency.

- Some agencies are very responsive to regulations and standards established under contract, others are not. The apparent control inherent in the option to not renew a contract is largely vitiated by the acute burden placed upon the agency's patients by such a step, and, more potently, by the political pressure which may rapidly and effectively be brought to bear by often prestigious members of the agency's lay board of directors.

- Standards which can be met by a majority of agencies must be established. There are many sensitive implications to the public evaluation of a private professional agency. It is not easy to measure the effectiveness of mental health services. Subjective factors of "professional quality" and quantitative measures of the numbers of "units of service provided" only roughly distinguish the "good" from the "bad" contracting agency once contracts are in force.

#### *Some problems encountered in the Los Angeles County contract experience:*

- There has been repeated difficulty in getting contract agencies to publicly acknowledge in their reports and other printed materials, the extent to which their programs are supported by state and county funds.

- There has been a tendency for some private agencies to develop direct access to elected officials and thereby circumvent the supervisory responsibility of County Administration.

- Federally funded programs have anticipated



that county and state funds would or should automatically replace declining federal grant funds. Often agencies that previously have been recipients of grants tend to have difficulty in grasping the many important distinctions between a grant and a contract.

- Individual contract agencies are sometimes unwilling or unable to recognize the fiscal limitations on increasing contract amounts in relation to the department's budget and responsibility to serve the total county of more than seven million people.

## Conclusion

There have been differing interpretations as to the meaning of the provision in the Lanterman-Petris-Short legislation which calls for the integrated use of all existing public and private mental health agencies and personnel in the new mental health system. Private agencies have understandably tended to regard this part of the law as mandating an extensive network of con-

tract services. The Los Angeles County Department of Mental Health has interpreted the law as encouraging the use of contracts, but as also requiring that agencies with funding sources other than those from Short-Doyle be maximally utilized. The number of contracts for mental health services executed by Los Angeles County with private mental health agencies has grown rapidly during the past year, because in the majority of instances the advantages as outlined above have outweighed the disadvantages. The policy on contracts developed by the Los Angeles County Department of Mental Health has had to be a suitable compromise among three factors: the desirability of contracting for services which the county cannot rapidly and economically provide, the need for maximum public accountability in the use of tax funds, and the pressure to "rescue" some private agencies from the adverse effects of a federal mental health program which had been established with little sensitivity to local planning and local fiscal realities.

## SMALL NEEDLES FOR SPINAL ANESTHESIA: FEWER HEADACHES

"Postspinal headache in the obstetrical patient can be prevented effectively by the use of very small needles. With needles of 16- or 18-gauge, used 20 years ago for continuous spinal anesthesia the incidence of headache was something like 30 to 40 and even as high as 50 percent. With a 20-gauge needle the incidence runs around 20 to 25 percent; with 22-gauge needles it drops to 10 percent; and with 26-gauge needles the incidence ranges from 1 to 5 percent. Some have reported an incidence even lower than 1 percent. So it is obvious that the best way to prevent this problem is to use a very small needle. Adequate hydration should be maintained, too, because the great loss of fluid during delivery may contribute to the development of cerebrospinal hypotension . . ."

—JOHN J. BONICA, M.D., Seattle

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 16, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Immunization and Health Information for International Travel

THE COMMUNICABLE DISEASES to which persons may be exposed while traveling abroad vary with the countries in which they stay or through which they pass, the duration of their journey or stay and the occurrence of local or seasonal epidemics. The risk can be readily circumvented by immunization in many instances. Some immunizations are required to enter or reenter a country (smallpox, cholera, yellow fever), while others are only recommended but not required for entry or reentry.

This report deals with recommended immunizations. The diseases which are reviewed here often pose a more serious threat to the traveler's health and enjoyment of his journey than the quarantinable diseases. Travelers should give serious consideration to these recommended immunizations and preventive measures in preparing for a trip abroad. Some of the recommendations apply to all overseas travel while others are indicated only in specific situations. The recommended immunizations are based on information obtained from the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics and are offered for the traveler's protection.

*Travelers' Diarrhea.* Diarrhea is probably the most common disease of travelers, yet the cause remains an enigma. Though travelers' diarrhea is known the world over, it is clearly more prevalent in tropical and subtropical areas, where it seems related to poor sanitation and hygiene.

What precautions can be recommended for the traveler? Water is usually safe in larger cities and at hotels accustomed to international travelers. If water is of questionable safety for drinking, use of the same water for making ice or for brushing teeth presents an equal hazard. If there are any doubts about the safety of the water, one should consider using bottled water or water from the hot water tap, provided that the water is sufficiently hot so that the hand must be withdrawn. Foods may present special hazards in certain areas of the world, particularly raw fruit and vegetables, dairy products, and raw shellfish.

As for chemoprophylaxis for travelers' diarrhea, there is no unanimity of opinion. Nor is there good evidence to support the use of antibacterial agents although Entero-vioform® has been used successfully to prevent such gastrointestinal disease as amebiasis and possibly shigellosis in mental institutions. At present, no chemoprophylaxis is routinely recommended for travelers.

For symptomatic treatment of nonspecific travelers' diarrhea, physicians might consider providing paregoric, Lomotil® (diphenoxylate), or Kaopectate® (kaolin-pectin) for their traveling patients.

Until the cause or causes of this disease entity are better defined, "turista" will continue to be an uninvited companion of many travelers.

*Tetanus and Diphtheria.* Tetanus and diphtheria are ubiquitous. No areas of the world are free of these frequently fatal infections. The



usual schedule recommended by the American Academy of Pediatrics or the Public Health Service Advisory Committee on Immunization Practices provides adequate protection for children. Adults should receive booster doses of tetanus-diphtheria toxoid (adult type) every 10 years.

*Poliomyelitis.* The incidence of poliomyelitis has been greatly reduced in the United States, Australia, New Zealand, Canada and Western Europe in recent years but remains a major problem in most other countries of the world. Adequate immunization is strongly recommended for all international travel. Although the need for an additional single dose of trivalent oral poliovirus vaccine (OPV) has not been established, children who have completed the accepted primary course of OPV should receive a single booster dose. Adults who received fewer than two doses of OPV should have two doses, six to eight weeks apart before departure. Adults who have had two or three doses of OPV should receive a single dose. This latter booster need never be repeated for subsequent travel.

*Measles (Rubeola or Eight-Day Measles).* For children who have not had measles nor have been vaccinated against measles, measles vaccine is recommended.

*Typhoid Fever.* Typhoid vaccine is not recommended for travelers who stay at the usual tourist accommodations in most European and Caribbean countries. Immunization is advised for travelers going to areas where typhoid is currently an epidemic or endemic problem (Central America, South America, Africa, Asia, the Middle East and the Pacific Region).

*Plague.* Routine immunization is not indicated for tourists going to countries reporting human or animal infections. Immunization is advisable for all persons traveling to Vietnam, Cambodia and Laos. Persons whose occupations or field work brings them into frequent or regular contact with wild rodents in enzootic areas in South America, Africa or Asia should also receive the vaccine. Booster doses should be given every six to 12 months for as long as opportunity for exposure exists.

*Typhus fever.* The rarity of epidemic louse-borne typhus minimizes the need for immunization. The disease presently is found only in rural or remote highland areas of Ethiopia, Rwanda, Burundi, Mexico, Bolivia, Ecuador, Peru and

mountainous areas of Asia. Even there, however, the risk of typhus for United States travelers is extremely low. Immunization against typhus is not required by any country as a condition for entry. Typhus immunization is suggested only for such persons as scientific investigators, oil field and construction workers, missionaries and some government workers who live in or visit areas where the disease actually occurs or who will be in close contact with the indigenous population in such areas. Booster doses should be given at intervals of six to twelve months for as long as the opportunity for exposure exists.

*Rabies.* Preexposure rabies prophylaxis is not recommended for tourists. However, persons (especially children) living in areas where rabies is a constant threat (Africa, Asia and parts of South and Central America) should be considered for preexposure rabies prophylaxis. Duck embryo rabies vaccine is the agent of choice.

*Influenza.* Routine use of influenza vaccine is not recommended. During epidemic years its use may be considered, especially for travelers with chronic debilitating conditions such as congenital and rheumatic heart disease; cardiovascular disorders, particularly with evidence of cardiac insufficiency; chronic broncho-pulmonary disease, and chronic metabolic disorders such as diabetes mellitus. Candidates for influenza vaccine who have had severe or local systemic reactions to the vaccine in the past may experience less discomfort if the newly available highly purified vaccine is used.

*Infectious Hepatitis.* A vaccine for immunization against infectious hepatitis is not available, but passive immunization with immune serum globulin (ISG) is effective for temporary prophylaxis against infectious hepatitis.

The risk of infectious hepatitis for United States residents traveling abroad varies with living conditions and the prevalence of hepatitis in the areas to be visited. Travelers may be at no greater risk than in the United States when their travel involves ordinary tourist activities and little exposure to uncooked foods or water of uncertain quality. For these travelers, ISG is not recommended.

For travelers visiting areas where hepatitis is a major health problem who may be exposed to infected persons and to contaminated food and water, there is increased risk of acquiring hepatitis. A single dose of ISG is recommended. A

simplified dosage guideline is: up to 50 pounds, 0.5 ml; between 50 and 100 pounds, 1.0 ml; and over 100 pounds, 2.0 ml. For extended travel (greater than two months) doubling the dose is recommended with repeat administration every six months for those residing in endemic areas.

**Malaria.** Malaria remains a highly prevalent and serious endemic disease in many tropical and subtropical countries. In recent years a number of United States travelers have acquired malaria while traveling abroad because they have not received adequate chemoprophylaxis. Endemic areas where prophylaxis may be needed include Africa; Haiti; Central America; the Southern West Coast Region and Southern States of Mexico; South America with the exception of Venezuela, Chile and Argentina; the Southern Middle East; Southeast Asia, Korea and some islands of the Western Pacific Region.

Although drug prophylaxis is usually recommended for persons residing in or traveling through countries in which malaria occurs, it should be recognized that the risk of malaria is not necessarily uniform throughout an entire country, and that local conditions to a large extent dictate the need for medication. The traveler's itinerary should be reviewed to determine whether it will take him into areas in which preventive measures are needed. The risk of life threatening *Plasmodium falciparum* malaria is especially high in both urban and rural areas of tropical Africa.

Chloroquine phosphate (Aralen®) is the drug recommended for general use as a chemosuppressive. In the United States it is available in 250 mg tablets. The adult dosage is two tablets (500 mg) once a week starting the week before possible exposure. Suppression should be continued at this dosage throughout the time spent in malarious areas, and for six weeks thereafter.

The regimen described above will provide complete protection against *Plasmodium falciparum*, with the exception of those strains in Southeast Asia and South America which are chloroquine-resistant. Infections caused by *P. vivax*, *P. malariae*, and *P. ovale* (relapsing species) are not prevented, but the symptoms are suppressed.

Primaquine phosphate is the drug used for radical cure of relapsing species of malaria. The

adult dosage is 26.3 mg (15 mg base) daily for 14 days following return from a malarious area. The routine use of primaquine for all civilians who have been in a malaria endemic area is questionable. Intensity of exposure to relapsing species should determine its use. Primaquine may cause hemolysis in persons with glucose-6-phosphate dehydrogenase deficiency.

Alternate malaria suppressive drugs are listed in the *Control of Communicable Diseases in Man*, eleventh edition 1970, American Public Health Association. A pediatric dosage schedule for chloroquine phosphate can be found in the *Report of the Committee on Infectious Diseases 1970* ("Red Book") published by the American Academy of Pediatrics.

In addition to malaria chemoprophylaxis other common protective measures such as use of insect repellent, screening of doors and windows, and avoiding mosquito exposure at times of prime biting activity (dawn and dusk) should be stressed.

**African Sleeping Sickness (Trypanosomiasis).** During 1970, two imported cases of African trypanosomiasis (*Rhodesiense*) occurred in Californians. They had visited game parks in Rwanda and Botswana where they were severely bitten by tsetse flies (*Glossina*) shortly before onset of illness. Several other cases with similar African travel histories were reported from other areas in the United States during 1969 and 1970. Increasing tourism to trypanosomiasis endemic regions in West and East Africa portends additional cases in the future. No vaccine or practical means of chemoprophylaxis are available for protection of the traveler facing exposure to the tsetse fly vector. If exposure to biting tsetse flies in endemic trypanosomiasis areas cannot be avoided, the traveler should wear heavy protective clothing with long sleeves and long trousers and make use of helmets with mosquito netting attached for protection of the head and neck. Use of insect repellent may also be helpful.

All infectious diseases acquired by persons traveling abroad should be reported to the health department. Through such reporting, public health authorities will be aided in providing current and correct health information to guide and protect international travelers in their journeys.



# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**ALCOHOL & ALCOHOLISM**—Papers Presented at the International Symposium in Memory of E. M. Jellinek, Santiago, Chile—Edited by Robert E. Popham. Published for the Addiction Research Foundation by University of Toronto Press, Toronto 181, Ontario, 1970. 421 pages, \$15.00.

In August, 1966 an international symposium on alcohol and alcoholism was held in Santiago, Chile, as a memorial to the late Dr. E. M. Jellinek, recognized as one of the leading authorities in the field of alcoholism. Now, four years later, Robert E. Popham and the Addiction Research Foundation have selected for publication 50 of the most important papers presented at that symposium. They hoped to prepare a medical text on alcohol and alcoholism suitable for those students and physicians interested in research, treatment, education and program development. Unfortunately the text falls far short of its goals and can not be considered the up to date, definite text in this important field.

The text does have certain areas of merit. The tributes to Dr. Jellinek give added perspective to the alcoholism problem. The multi-authored sections give needed depth to many important specialized research areas. It is especially interesting to read the translated papers of Central and South American specialists who participated in the symposium, since they rarely publish in standard English journals. Unfortunately, the presentation of papers is often unsuitable for teaching and at times becomes too specialized for the average reader. The papers presented on the metabolism of alcohol at high altitudes, the biochemical studies of the "anti-alcohol drug" (metronidazole), important genetic factors in alcoholism and epidemiological study of alcoholism in Latin America, are especially informative and interesting. However, the major drawbacks of the text are that the research format presentation has not been uniformly edited and the authors have attempted to update this 1966 conference simply by adding minor footnotes to key topics.

Critical advances in this field over the past four years are covered only in passing or added as brief footnotes to longer sections. Recent topics that deserved more discussion include the effect of alcohol on the metabolism of other drugs, alcohol effect on intestinal absorption and function, possible important biochemical parameters of alcohol addiction, the physiological bases for alcohol withdrawal, sleep disturbances in alcoholism, adrenal pituitary responses to alcohol, newer drug treatment of the alcohol withdrawal syndrome and the important development of animal models for alcohol withdrawal. Especially lacking to the clinician who is interested in alcoholism is the absence of a presentation of the effects of alcohol on carbohydrate metabolism. Thus, although the text may be valuable to a limited audience, it does not achieve the desired scope this topic deserves.

CHARLES E. BECKER, M.D.

**ANTIMICROBIAL THERAPY**—Benjamin M. Kagan, M.D., F.A.A.P., F.A.C.P., Director, Department of Pediatrics, Consultant, Department of Medicine, Cedars-Sinai Medical Center; Professor of Pediatrics, University of California, Los Angeles; with Contributions by 46 Authorities. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 500 pages, \$14.50.

Every few years the *Pediatric Clinics of North America* issues a volume in which antimicrobial therapy is discussed. Such volumes appeared in 1956, 1961 and 1968. The authors of individual chapters in the 1968 volume were asked in 1969 to bring their presentations up to date so that they could be compiled as a separate independent volume on antimicrobial therapy, under the editorship of Dr. B. Kagan of Los Angeles. The first half of the present book thus is an updated version of the 1968 *Pediatric Clinics* volume and the changes in the discussion of individual drugs are relatively minor. In the second half of the book "clinical applications" are discussed. Ten sections have been added here, dealing with antimicrobial agents in orthopedics, in burns, in trauma, in ophthalmology, in dermatology and in other specialized infection problems. Thus the present, 1970 version is a reasonably complete and fairly up-to-date reference book for antimicrobial therapy listing the preferences and prejudices of each author. There is some emphasis on the use of antimicrobial drugs in infants and children and a useful chapter on dosage is appended. Inevitably there is some repetition (e.g. of side effects of drugs) and some discrepancies in recommended uses can be noted. Inevitably also, the life span of specific listed recommendations will be short as microorganisms change in their resistance patterns and new drugs arrive on the market.

In spite of these limitations the book appears to be a useful reference work which can help physicians in selecting antimicrobial drugs for specific indications and in guarding patients against some untoward effects—at least in 1970.

ERNEST JAWETZ, M.D.

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**FROZEN BLOOD**—A Review of the Literature 1949-1968—Arthur R. Turner, M.D. Gordon and Breach, Science Publishers, Inc., 150 Fifth Avenue, New York, N.Y. (10011), 206 pages; \$19.50 for Reference, prepaid \$15.60; \$10.00 for Professional, prepaid \$8.00.

Readers looking for a well-organized, informative, authoritative summary of the current state of the art of freezing red cells will not find it here. This book tells who said what, when, where—each paper summarized in a sentence or two. Equal attention is given to articles old and new, whether they summarize years of experience or are a Master's thesis. An attempt is made to arrange the material in logical headings; however, as recognized by the compiler, the complex interrelationship of the many variables which affect the red cells inevitably leads to confu-



sion. Within each section the discussion cannot follow a consistent direction since one paper at a time is summarized.

This book may be of some use to a beginning investigator in the field, in that it provides a list of publications which includes those he will want to read.

HERBERT A. PERKINS, M.D.

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**MEDICAL READINGS ON DRUG ABUSE**—Oliver E. Byrd, Stanford University. Addison-Wesley Publishing Company, Inc., Reading, Mass. (01867). 1970. 274 pages, \$3.95.

Dr. Byrd's latest book is, in essence, a small library of condensed articles covering a wide spectrum of published papers relating to the abuse and use of dangerous drugs. This indexed work consists of some 180 contributions to current medical literature. It covers subjects ranging from the affects of the drugs per se to reviews of official stands of various medical groups on specific drugs and/or the drug problem in general.

This is not a permissive book; in fact those seeking material to justify improper use of drugs whether tobacco, alcohol, marijuana or barbiturates, opiates or stimulants will be disappointed. Those seeking conservative material pertinent to the current drug abuse scene, however, will find this paperback a welcome addition to their library.

EDWARD R. BLOOMQUIST, M.D.

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**A GUIDE TO DERMATOHISTOPATHOLOGY**—Herman Pinkus, M.D., Professor and Chairman, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Attending Dermatologist, Detroit General Hospital; Chief, Dermatology Section, Veterans Administration Hospital, Allen Park, Michigan; and Amir H. Mehregan, M.D., Adjunct Associate Professor, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Associate Dermatologist, Detroit General Hospital. Appleton-Century-Crofts, Division of Meredith Publishing Company, 440 Park Avenue South, New York, N.Y. (10016), 1969. 546 pages, \$20.00.

The new text *A Guide to Dermatohistopathology* by Pinkus and Mehregan is the first guide to skin pathology that is easily readable. It is a welcome addition to both dermatologist and pathologist due to its clarity of explanation.

Pinkus and Mehregan discuss basic normal anatomy, techniques of pathology and methods of organizing observations under the microscope. These authors then proceed through inflammatory, granulomatous, metabolic, connective tissue, pigmentary diseases and then tumors. Each individual tumor and disease process is discussed simply and with reference to the 403 photomicrographs and charts.

The section on granulomas is divided into predominately mononuclear and mixed cell granulomas, a classification that allows easy categorization. The tumor section is well illustrated and the differences between appendageal tumors are easily seen. Many of the descriptions are delightful to read especially on differentiation of lichen planus and lupus erythematosus and the section on artefacts seen in tissue.

This book is a gem in the wealth of knowledge on the interpretation of pathology of the skin.

LEO INDIANER, M.D.

**TECHNIQUES IN CLINICAL PHYSIOLOGY—A Survey of Measurements in Anesthesiology**—Edited by J. Weldon Bellville, M.D., Professor of Anesthesia, Stanford University School of Medicine; and Charles S. Weaver, Ph.D., Research Engineer, Stanford Electronics Laboratories; Research Associate, Department of Anesthesia, Stanford University School of Medicine. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1969. 532 pages, \$20.00.

With the numerous tools and techniques now available for physiologic measurements, the clinician or researcher may puzzle over which is best for his particular task. Planning to monitor breath-to-breath inspired oxygen concentration in a halothane-oxygen mixture, it would be well to know that monitors using either thermo-conductivity or the fuel cell principle are totally inappropriate. The former is inappropriate because of the slow response time, and the latter because of the halothane induced measuring error.

Bellville and Weaver have edited a book which will help answer this kind of question. The book is diverse in its coverage with contributions from physicians, engineers, mathematicians and chemists. The cohesive bond between the men is that nearly all have worked in or with the Department of Anesthesia at Stanford University. Because of the diversity in the contributors' disciplines, the emphasis found in individual chapters varies. Some have stressed the monitoring of physiologic systems while others emphasized specific tools. Some shied away from mathematics in their presentation while others liberally sprinkled their dissertations with formulas. For me, an anesthesiologist, the chapters relating to cardiac function evaluation, gas and blood gas analysis, and gas chromatography were the most useful. Other readers may equally well appreciate chapters on basic electronics, computers or radioisotope techniques. The authors have added short comments to most of their references enabling the reader to determine, at a glance, whether a particular reference is of value to him. I believe the book contains valuable material, not only for the researcher and clinician, but also for the resident in anesthesia who would like a more in-depth discourse in the tools and techniques of his science.

LEONARD F. WALTZ, M.D.

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**ABORTION: LAW, CHOICE AND MORALITY**—Daniel Callahan. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1970. 524 pages, \$14.95

This is essentially a textbook on the enormous worldwide problem of abortion. It has an extensive bibliography, and supplies a mass of data. Dr. Callahan (Ph.D.) focuses on the moral problems of abortions, integrated with the medical, social and legal questions. He stresses the diversity of values in a pluralistic society, and the influence of personal bias on each individual's attitude. All abortion decisions will be influenced by one's personal morality.

I must agree with Dr. Alan Guttmacher that this book is a must for all concerned with a humane solution of the abortion problem. I hope the California Medical Association will make this available to all of our legislators.

GEORGE K. HERZOG, JR., M.D.



# In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ALDEN, CHARLES, Los Angeles. Died October 27, 1970 in Los Angeles of kidney disease, aged 71. Graduate of Université de Genève Faculté Médecine, 1929. Licensed in California in 1943. Doctor Alden was a member of the Los Angeles County Medical Association.

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BALOGH, STEFAN H., San Diego. Died October 14, 1970 in San Diego of malignant lymphoma, aged 66. Graduate of Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, 1927. Licensed in California in 1958. Doctor Balogh was a member of the San Diego County Medical Society.

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BEHNEMAN, HAROLD MAYO F., San Diego. Died November 3, 1970 in San Diego, aged 75. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1927. Doctor Behneman was a member of the San Diego County Medical Society.

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BRUSON, SOLOMON, Los Angeles. Died November 17, 1970 in Palm Springs of pneumonitis, aged 65. Graduate of University of Cincinnati College of Medicine, 1929. Licensed in California in 1929. Doctor Bruson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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BURKE, GEORGE TREBLE, Ventura. Died November 8, 1970 in Ventura, aged 66. Graduate of McGill University Faculty of Medicine, Montreal, 1931. Licensed in California in 1932. Doctor Burke was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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COLEMAN, WARREN R., Carmichael. Died September 5, 1970 in Sacramento, aged 59. Graduate of University of Oregon Medical School, Portland, 1941. Licensed in California in 1946. Doctor Coleman was a member of the Sacramento County Medical Society.

DIDDY, GORDAN A., Fresno. Died November 18, 1970 in Fresno, aged 59. Graduate of State University of Iowa College of Medicine, Iowa City, 1938. Licensed in California in 1941. Doctor Diddy was a member of the Fresno County Medical Society.

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DONOHUE, PAUL JOHN, Los Angeles. Died October 28, 1970 in Los Angeles of carcinoma of the larynx, aged 61. Graduate of Kirksville College of Osteopathy and Surgery, Kirksville, Missouri, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Doctor Donohue was a member of the Los Angeles County Medical Association.

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FELLOWS, RUDY LEE, (Fresno). Died November 7, 1970 in Fresno, aged 39. Graduate of Howard University College of Medicine, Washington, D.C., 1963. Licensed in California in 1964. Doctor Fellows was a member of the Fresno County Medical Society.

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GRAY, ETTA, Claremont. Died October 24, 1970 in Pomona of cerebral hemorrhage, aged 89. Graduate of Cooper Medical College, San Francisco, 1906. Licensed in California in 1906. Doctor Gray was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

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HAGGE, NOOMI EBBA, San Francisco. Died May 9, 1970 of endometrial carcinoma, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1943. Licensed in California in 1943. Doctor Hagge was a member of the San Francisco Medical Society.

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HARDING, HENRY WILBUR, Oakland. Died November 24, 1970 in Oakland, aged 80. Graduate of College of Physicians and Surgeons, Los Angeles, 1914. Licensed in California in 1914. Doctor Harding was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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HENRY, ARCHIE WARD, San Leandro. Died October 29, 1970 in San Leandro of arteriosclerotic heart disease, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1926. Doctor Henry was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

HESEL, VICTOR E., Los Angeles. Died October 9, 1970 in Holt, Missouri, of coronary artery disease, aged 73. Graduate of University of Arkansas School of Medicine, Little Rock, 1927. Licensed in California in 1928. Doctor Hessel was a member of the Los Angeles County Medical Association.

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HOMME, OWEN HALVOR, Los Angeles. Died October 31, 1970 in Los Angeles of heart disease, aged 74. Graduate of Rush Medical College, Chicago, 1925. Licensed in California in 1926. Doctor Homme was a member of the Los Angeles County Medical Association.

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LOUNSBERRY, C. RAY, San Diego. Died October 31, 1970 in San Diego, aged 82. Graduate of St. Louis University School of Medicine, 1918. Licensed in California in 1925. Doctor Lounsberry was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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POSSON, CHARLES R., Long Beach. Died October 11, 1970 in Long Beach of cardiac arrest, aged 49. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Doctor Posson was a member of the Los Angeles County Medical Association.

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ROWE, ALBERT H., Oakland. Died October 30, 1970 in Piedmont of arteriosclerotic cardiovascular disease, aged 81. Graduate of University of California Medical School, Berkeley-San Francisco, 1914. Licensed in California in 1914. Doctor Rowe was a member of the Alameda-Contra Costa Medical Association.

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RUBENSTEIN, CHARLES LEO, San Francisco. Died November 8, 1970 in San Francisco, aged 75. Graduate of Harkov Medical Institute, Harkov, U.S.S.R., 1923. Licensed in California in 1933. Doctor Rubenstein was a member of the San Francisco Medical Society.

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SALA, RALPH DELLA, Oakland. Died October 30, 1970 in Berkeley of diabetic glomerulosclerosis, aged 77. Graduate of Tufts College Medical School, Boston, 1924. Licensed in California in 1936. Doctor Sala was a member of the Alameda-Contra Costa Medical Association.

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SHAHER, FREDERICK P., Los Angeles. Died November 18, 1970 in Los Angeles of cerebrovascular accident, aged 77. Graduate of University of California Medical School, Berkeley-San Francisco, 1921. Licensed in California in 1921. Doctor Shafer was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Association.

SLOAN, LEONARD NORMAN, Sherman Oaks. Died November 12, 1970 in Sherman Oaks of rheumatic heart disease, aged 66. Graduate of The University of Minnesota Medical School, Minneapolis, 1925. Licensed in California in 1927. Doctor Sloan was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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SONNENBERG, ALVIN FRED, El Monte. Died October 25, 1970 in Bradbury of lung cancer, aged 53. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1942. Licensed in California in 1942. Doctor Sonnenberg was a member of the Los Angeles County Medical Association.

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VAN FLEET, WILLIAM C., Apple Valley. Died October 16, 1970 in an airplane crash at Sidney, Nebraska, aged 43. Graduate of University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1955. Doctor Van Fleet was a member of the San Bernardino County Medical Society.

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VENIS, KEMPER NIHIL, Los Angeles. Died November 6, 1970 on a boat near Catalina of heart disease, aged 57. Graduate of Eclectic Medical College, Cincinnati, 1938. Licensed in California in 1964. Doctor Venis was a member of the Los Angeles County Medical Association.

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WAGNER, WILLIAM FRANKLYN, Long Beach. Died November 5, 1970, in Long Beach of coronary artery disease, aged 56. Graduate of The University of Nebraska College of Medicine, Omaha, 1943. Licensed in California in 1951. Doctor Wagner was a member of the Los Angeles County Medical Association.

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WALTERS, WESLEY R., Colfax. Died April 27, 1970 of fatty metamorphosis of liver, aged 53. Graduate of Northwestern University Medical School, Chicago, 1944. Licensed in California in 1945. Doctor Walters was a member of the Placer-Nevada County Medical Society.

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WORO, BENJAMIN, San Diego. Died September 5, 1970 in La Mesa of arteriosclerosis, aged 60. Graduate of Temple University School of Medicine, Philadelphia, 1933. Licensed in California in 1938. Doctor Woro was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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YOST, NANCY C., Glendale. Died October 26, 1970 in Los Angeles of myocardial infarction, aged 53. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1951. Licensed in California in 1951. Doctor Yost was a member of the Los Angeles County Medical Association.



# Proposed CMA Constitutional Amendments

## FOR ACTION IN 1971

Three Constitutional amendments were introduced in the 1970 House of Delegates. One amendment was withdrawn by the author. Under the terms of the Constitution, the remaining two amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

### COMPOSITION OF COUNCIL ARTICLE III, SECTION 9

**Constitutional Amendment 1-70**      **Committee C**  
Introduced by: Simon Brumbaugh, M.D.  
Representing: San Diego County Medical Society

WHEREAS, the growth in medical population in California has continued to increase at a rapid rate; and

WHEREAS, the size of the CMA Council has increased with the size of the medical population; and

WHEREAS, the efficiency of the Council decreases with increase in size; and

WHEREAS, the expense of maintaining the Council increases with size; now, therefore, be it

*Resolved:* That Article III, Section 9 of the Constitution of this Association be amended by deleting the figures in parentheses and adding the figures in italics, so that this Section will read as follows:

"The Council shall consist of:

(a) Elected councilors from the councilor districts set forth in Section 10. Each councilor district shall be entitled to elect one councilor for each (1,000) *1,500* active members, or major fraction thereof, according to its membership as of the first day of September of the preceding

year; provided, that each councilor district shall be entitled to a minimum of one councilor"; and be it further

*Resolved:* That the Council through its committees review the ratio of membership to councilor representation each five years; and be it further

*Resolved:* That the Council be empowered to change this ratio after such review each five years as necessary for efficiency and economy.

### COMPONENT MEDICAL STUDENT SOCIETY ARTICLE I, SECTION 4, AND ARTICLE III, SECTION 7(a)

**Constitutional Amendment 2-70**      **Committee C**  
Introduced by: E. Kash Rose, M.D.

WHEREAS, medical students of Schools of Medicine in California have demonstrated a desire to be increasingly involved in the activities of the medical profession in California generally, and the activities of the California Medical Association specifically; and,

WHEREAS, such involvement of medical students in these activities may offer significant and mutual benefits to the California Medical Association and to the medical students; and,

WHEREAS, this involvement and the anticipated mutual benefits might best be encouraged and achieved through the formation of a new component society to be known as the "Component Medical Student Society"; and,

WHEREAS, the California Medical Association will be evaluating this and other proposals during the coming year; and,

WHEREAS, if this evaluation suggests that the California Medical Association form a "Component Medical Student Society," certain amendments to the Constitution will be necessary; and

WHEREAS, the anticipatory introduction at this time of such necessary amendments to the Constitution will serve the next House of Delegates

should it wish to charter a "Component Medical Student Society" by satisfying the "one year time requirement" as specified in Article VIII, Section 3 of the Constitution; therefore, be it

*Resolved:* That the Constitution of this Association be amended as follows:

1. That Article I, Section 4 of the Constitution of this Association be amended by deleting the word in parentheses and by adding the words in italics, so that this section shall read:

"Component societies include all county medical societies, which may cover one or more counties, (or) any established component district of at least 300 members of a county society which has exercised option to withdraw from that county society and set up a separate component

society, heretofore or hereafter, chartered by this Association, *or a Component Medical Student Society consisting of bona fide medical students at accredited Schools of Medicine in California.*"

2. That Article III, Section 7(a) of the Constitution of this Association be amended by deleting the word in parentheses and by adding the words in italics, so that this section shall read:

"(a) The House of Delegates shall issue charters to medical societies of any county, any component society of at least 300 members which has exercised its option to become autonomous, (or) to any group of counties deemed eligible which have made proper application therefor *or to a Component Medical Student Society.*"

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# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(Formerly WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

**THIS BULLETIN** of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a National Institutes of Health grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ADOLESCENT MEDICINE

January 29-31 — Adolescent Medicine — Alienation, Ours and Theirs. USC at Frontier Hotel, Las Vegas. Friday-Sunday. \$85.

February 13—Adolescent Medicine 1971, Fact and Fancy. Childrens Hospital of Orange County, Orange. Saturday. \$3. Contact: Merl J. Carson, M.D., Childrens Hospital of Orange County, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

## ALCOHOLISM AND DRUG USE

January 30-31—Sex and Drug Scenes Today. See Psychiatry, January 30-31.

## CANCER

January 15-16—Current Concepts of Medical Oncology. Mt. Zion Hospital at Sir Francis Drake Hotel, San Francisco. Friday-Saturday. Basic Sciences, Endocrine Responsive Tumors, Leukemia/Lymphoma, Supportive Medical Therapy. \$40. 12 hrs. Contact: Mrs. Ann Raisbeck, Medical Cancer Service, Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 567-6600, ext. 196.

February 10 — Pitfalls in Cancer Management. PMC. Wednesday.

Continuously—Tumor Board—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 2-3 p.m. Advice and consultation

from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## MEDICINE

January 16—Clinical Gastroenterology. Marys Help Hospital, Daly City. Saturday. Contact: Staff Secretary, Gastroenterology, Marys Help Hospital, 1900 Sullivan Ave., Daly City 94105. (415) 992-4000.

January 20—15th Annual Midwinter Symposium for Researchers. Los Angeles County Heart Association at Hilton Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Joyce Martin, Program Associate, LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California, San Francisco Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

- January 20-22—**Postgraduate Symposium on Pediatric Endocrinology.** American Academy of Pediatrics at Memorial Hospital of Long Beach, Long Beach. Wednesday-Friday. 8 hrs. Contact: H. David Mosier, Jr., M.D., Professor of Pediatrics, UCL (714) 663-9393, ext. 595.
- January 23—**Therapeutic Problems in Endocrinology.** PMC. Saturday.
- January 26-28—**Third Annual Cerebral Function Symposium.** Annual Cerebral Function Symposium at Hotel del Coronado, Coronado. Tuesday-Thursday. Hemispherectomy and Cerebral Function. \$50. 18 hrs. Contact: W. Lynn Smith, Ph.D., The Annual Cerebral Function Symposium, Franklin Medical Center, 2045 Franklin, Suite 1120, Denver 80205. (303) 534-0903.
- January 27—**New Techniques in Diagnosis and Treatment of Cerebral Vascular Disease.** LLU. Wednesday. \$25. 8 hrs.
- January 30—**Pathogenesis and Management of Fluid and Electrolyte Imbalance.** PMC. Saturday.
- February 1-12—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- February 3—**Recent Advances and Techniques of Cardio-Pulmonary Resuscitation.** UCSD at University Hospital of San Diego County, San Diego. Wednesday. \$5. 4 hrs.
- February 5-6—**Evaluation and Management of Neuromuscular Diseases.** UCD at Sahara Tahoe Hotel, Lake Tahoe. Friday-Saturday. Clinical and Laboratory Evaluation of Weakness and Hypotonia; Clinical and Pathologic Characteristics of Central Neuronal Muscular Atrophies, Polyneuropathies, Dystrophic Myopathies, Inflammatory Myopathies and Congenital Myopathies. General Approaches to Management of Pain, Weakness and Deformity; Management of Progressive Conditions; Management of Static and Transient Conditions; Special Aspects of Rehabilitation in Children; Psychological and Vocational Aspects of Rehabilitation of Patients. \$40. 11 hrs.
- February 12-13—**American College of Physicians—Northern California and Nevada Regional Meeting.** Fairmont Hotel, San Francisco. Friday-Saturday. \$5. 11 hrs. Contact: John R. Gamble, M.D., Governor for Northern California and Nevada, ACP, 655 Sutter Street, San Francisco 94102. (415) 673-4080.
- February 17-19—**Medical Complications in Pregnancy.** See Ob-Gyn, February 17-19.
- February 19-20—**American College of Physicians—Southern California Regional Meeting.** Friday-Saturday. Contact: Edward E. Boland, M.D., Governor for Southern California, ACP, 321 N. Larchmont Blvd., Los Angeles 90004. (213) 462-1281.
- February 20—**Intensive Medical Care Symposium.** STAN. Saturday. Shock, thromboembolism, tachyarrhythmias, respiratory failure, bleeding disorders, disseminated intravascular coagulation and fibrinolysis, drug injection, hazards of intensive care.
- February 24-25—**Critical Care Medicine and Circulatory Shock.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. \$65.
- February 24-26—**7th Annual Course on the Evaluation of Pulmonary Function.** Tuberculosis and Respiratory Disease Association of California at Town and Country Inn, Mission Valley, San Diego. Wednesday-Friday. \$100 members of American Thoracic Society, \$125 others. 24 hrs. Contact: Miss Louise Ratchiff, TARDAC, 424 Pendleton Way, Oakland 94621. (415) 636-1756.
- February 25-27—**Pediatric Nephrology.** See Pediatrics, February 25-27.
- February 26-27—**The Office Care of Dermatologic Disorders.** STAN. Friday-Saturday.
- February 27—**Advances in Diagnosis and Treatment of Angina Pectoris.** PMC. Saturday. 8 hrs.
- February 28—**Hypertension—Fifth Annual Leon Wolpe Memorial Lecture.** Hollywood Community Hospital at Sheraton-Universal Hotel, Universal City. Sunday. Contact: William Grasske, M.D., Hollywood Community Hospital, 6245 De Longpre Ave., Hollywood 90028. (213) 462-2271.
- March 1-19—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.
- March 1-12—**Coronary Care Unit Program for Physicians.** See Medicine, February 1-12.
- March 4-6—**Intensive Care Unit: A Team Approach.** PMC. Thursday-Friday.
- March 4-6—**Treatment of Neonatal Pulmonary Disease.** See Pediatrics, March 4-6.
- March 5—**Evaluation of Myocardial Function.** USC at Hilton Hotel, Pasadena. Friday. \$35.
- March 7-12—**Arrhythmia Retreat.** USC at Erawan Garden Hotel, Indian Wells. Sunday-Friday. \$200.
- March 11-13—**Neurology: Recent Advances.** UCSF. Thursday-Saturday.
- March 12—**Electromyography Symposium.** USC. Friday.
- March 13—**Recognition of Levels of Unconsciousness in the Comatose Patient.** PMC. Saturday.



March 13-14—**Antibody Identification: Problem Cases.** UCSF at Irwin Blood Bank, San Francisco. Saturday-Sunday.

March 13-14—**Geriatric Workshop—Problems of the Elderly.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 14-17—**Current Topics in Gastrointestinal Disease.** UCLA at El Mirador Hotel, Palm Springs. Sunday-Wednesday.

March 14-18—**American College of Allergists—Annual Meeting and Pre-Congress Seminar.** Fairmont Hotel, San Francisco. Sunday-Thursday. \$10 nonmembers. Contact: Eloi Bauers, Exec. Vice-Pres., ACA, 2100 Dain Tower, Minneapolis 55402. (612) 332-2948.

Continuously—**Coronary Care.** St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—**Coronary Care Unit Training for Physicians.** CRMP Area VI and San Bernardino County General Hospital at San Bernardino County General Hospital. Four week courses at monthly intervals, scheduled by arrangement. For practicing physicians working in and directing CCU's. Bedside care, electrocardiography, physical diagnosis, clinical history, therapy, insertion of pacemakers, cardioversion. 160 hrs. Contact: Carl L. Cook, Jr., M.D., San Bernardino County General Hospital, 780 E. Gilbert St., San Bernardino 92404. (714) 885-3411.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSFB, 4200 California St., San Francisco 94118. (415) 387-0934.

Continuously—**Medico-Surgical Cardiovascular Seminar.** STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

Continuously—**Cardiology Conferences—CRMP Area III.** Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 84304. (415) 321-1200, ext. 6015.

## **Grand Rounds—Medicine**

### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

### **Wednesdays**

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

### **Thursdays**

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

## Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

11:30 a.m., First Floor Auditorium, Room 13-105, UCLA Medical Center. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

## Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

## Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

## MENTAL RETARDATION

February 8-19—**Mental Retardation Workshop.** UCLA and Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, recent research findings. 80 hrs. Contact: UCLA.

## OBSTETRICS AND GYNECOLOGY

January 22-24—**Therapeutic Abortion—Implementation.** UCLA. At International Hotel, Los Angeles. Friday-Sunday.

February 6—**The Role of the Community Hospital—Obstetric Services.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday. Obstetrical Anesthesia, The Newborn in the Delivery Room, Nursery ICU, New Role of the Laboratory in Perinatal Care, Maternal Factors Affecting Fetal Welfare, Fetal ECG Interpretation, Applications of Ultrasound and its Limitation in Obstetrics, Teenage Pregnancy Clinic, High Risk Pregnancy Clinic. \$30. 7 hrs.

February 6-7—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Amenorrhea, Steroid Therapy, Genetics, Induction of Ovulation, IUD, Abortion, Sterilization, Breast Cancer, Resuscitation of the Newborn, Small for Dates Baby, Ovarian Cancer. \$30. 14 hrs. Contact: Dee Davis, Exec. Sec., LAOGS, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 17-19—**Medical Complications in Pregnancy.** USC and the American College of Physicians at USC. Wednesday-Friday. Cardiovascular disease, hypertension, diabetes and anemia occurring in pregnancy. Contact: USC.

March 6—**Therapeutic Abortion.** PMC. Saturday.

## Grand Rounds—Obstetrics and Gynecology

### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

## PEDIATRICS

January 20-22—**Pediatric Endocrinology.** See Medicine, January 20-22.

January 29-31—**Ninth Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 29-31.

February 11—**Tenth Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society and American Academy of Pediatrics, California Chapter II at Los Angeles County Medical Association Building, Los Angeles. Thursday. Emergency Treatment of the Newborn Infant in the Delivery Room. Contact: Mrs. Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 753-3704.

February 20-21—**Psychiatric Evaluation of the Child.** See Psychiatry, February 20-21.

February 23-25—**Conference on Hearing Screening on the Newborn.** Maternal and Child Service of HEW and Bureau of Maternal and Child Health, State Department of Public Health. Hilton Inn, San Francisco International Airport. Tuesday-Thursday. Contact: Edith Krabach, Bureau of Maternal and Child Health, State Department of Public Health, 2151 Berkeley Way, Berkeley 94704. (415) 843-7900.

February 25-27—**Pediatric Nephrology.** UCSF. Thursday-Saturday. 13½ hrs.

February 26-28—**Second Annual Southern California Pediatric Postgraduate Course.** American Academy of Pediatrics, Chapter II, District IX; Childrens Hospital of Orange County; Los Angeles Pediatric Society; Southwestern Pediatric Society; and Childrens Hospital of Los Angeles at El Mirador Hotel, Palm Springs. Friday-Sunday. \$50. 15 hrs. Contact: Neil N. Litman, M.D., Program Chairman, 5830 Overhill Drive, Los Angeles 90043. (213) 291-1161.

March 4-6—**Treatment of Pulmonary Disease in Neonates.** UCI and CRMP Area VIII at Childrens Hospital of Orange County, Orange. Thursday-Saturday. Contact: Bruce D. Ackerman, M.D., Pediatric Pulmonary Demonstration Center, Dept. of Pediatrics, UCI.



## Grand Rounds—Pediatrics

### Tuesdays

- 8:00 a.m., Childrens Hospital Medical Center, Oakland.
- 8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.
- 8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.
- 8:30 a.m., Pathology Auditorium, San Francisco General Hospital.
- 12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

### Wednesdays

- 8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.
- 8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

### Thursdays

- 8:30-10:00 a.m., Room 664, Science Building, UCSF.
- 8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.
- 8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

### Fridays

- 8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.
- 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.
- 8:30 a.m., Room M104, Stanford University Medical Center, STAN.
- 8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.
- Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

## PSYCHIATRY

January 15-17—**The Family—A Bridge to the Community.** USC Division of Postgraduate Psychiatry at Erawan Garden Hotel, Indian Wells. Friday-Sunday. \$50. Contact: Donald H. Naftulin, M.D., Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

January 30-31—**The Sex and Drug Scenes Today.** University of California Extension, Riverside, at Sproul Hall, Riverside. Saturday-Sunday. \$37. 14 hrs. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

February 3-6—**American Group Psychotherapy Association.** International Hotel, Los Angeles. Wednesday-Saturday. Contact: Marilyn Schiff, AGPA, 1790 Broadway, New York 10019.

February 6—**Reality Therapy Workshop: Social Science for the 70's.** University of California Extension, Riverside, at Auditorium, Pacific High School, San Bernardino. Saturday. \$5. 4 hrs. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

February 15—**Psychodrama.** Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Mondays through March 22. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

February 20-21—**Psychiatric Evaluation of the Child.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

February 23—**Clinical Psychiatry.** UCLA. Tuesdays through May 11.

February 26-28—**Hypnosis: Therapy and Practice.** UCLA and American Society of Clinical Hypnosis, Education & Research Foundation. Friday-Sunday.

March 10—**Sex and Society in the Seventies.** LLU. Wednesday. \$25. 8 hrs.

March 12-13—**Suicide: Causes and Prevention.** University of California Extension, Riverside at Sproul Hall, Riverside. Friday-Saturday. \$26. 9 hrs. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

## Grand Rounds—Psychiatry

### Wednesdays

- 10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

## RADIOLOGY—PATHOLOGY

January 30-31—**Midwinter Radiological Conference.** Los Angeles Radiological Society at International Hotel, Los Angeles. Saturday-Sunday. Diagnosis, Therapy, Nuclear Medicine. \$30. Contact: J. Stanley Lance, M.D., 100 Congress St., Pasadena 91105. (213) 796-0381.

February 2-4—**Chest Radiology.** USC at El Mirador Hotel, Palm Springs. Tuesday-Thursday. \$125. 12 hrs.

March 8-12—**Diagnostic Radiology.** UCSF. Monday-Friday. For radiologists in clinical practice. Urinary, Pulmonary, Gastrointestinal, Pediatric Radiology. \$125. 25 hrs.

Continuously—**UCSF Radiology Rounds, Seminars, and Conferences.** Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiography Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

## Grand Rounds—Radiology-Pathology

### Mondays

- Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

## Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

## SURGERY—ANESTHESIOLOGY

January 18-22—Intensive Course in Otolologic Surgery. Los Angeles Foundation of Otology, USC and St. Vincents Hospital, Los Angeles. Monday-Friday. Otosclerosis surgery and chronic ear disease, inner ear problems, glomus tumors, facial nerve paralysis. \$300. Contact: Glenn R. Snyder, Managing Dir., Los Angeles Foundation of Otology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

January 23-24—Surgical Anatomy of the Orbit and Adnexa, Individual Dissection. USC and Research Study Club of Los Angeles at USC. Saturday-Sunday. Limited to applicants attending the Fortieth Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. \$50. 8 hrs. Contact: Dorothy Rundquist, Exec. Sec., RSCLA, 1622 Monterey Lane, No. 8, Huntington Beach 92649.

January 25-29—Fortieth Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. Research Study Club of Los Angeles at Hilton Hotel, Los Angeles. Monday-Friday. \$100. 46 hrs. Contact: Dorothy Rundquist, Exec. Sec., RSCLA, 1622 Monterey Lane, No. 8, Huntington Beach 92649.

January 29-31—Ninth Annual Clinical Conference in Pediatric Anesthesiology. Childrens Hospital of Los Angeles, Los Angeles. Friday-Sunday. \$75. 20 hrs. Contact: Wayne Herbert, M.D., Program Dir., CHLA, 4650 Sunset Blvd., Los Angeles 90054. (213) 663-3341.

January 30-31—Ninth Annual UCLA Symposium on Orthopedics: Total Hip Replacement. UCLA. Saturday-Sunday. Introduction and History of Total Hip Replacement, Skeletal Fixation, Indications for Total Hip Replacement, Complications of Total Hip Replacement—Systemic, Operating Room Environment, Bearing Analysis. \$125. 14 hrs.

January 31-February 3—Theodore Billroth Course in Surgical Anatomy. LLU. Sunday-Wednesday. \$175. 32 hrs.

February 1-6—Intensive Review, Orthopedic Surgery. J. Vernon Luck Research Society at Orthopedic Hospital, Los Angeles. Monday-Saturday. \$200. 56 hrs. Contact: Chad Smith, M.D., Orthopedic Hospital, 2400 South Flower St., Los Angeles 90007. (213) 747-4481, ext. 292.

February 6—Surgical Emergencies. PMC. Saturday.

February 12—Minor Vascular Repair. PMC. Friday.

February 26-27—Retinal Surgery. UCSF. Friday-Saturday. \$125. 13½ hrs.

March 5-6—American Society for Surgery of the Hand. Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Lee Milford, M.D., 869 Madison Avenue, Memphis, Tenn. 38104.

March 6-11—American Academy of Orthopedic Surgeons. Civic Auditorium, San Francisco. Saturday-Thursday. Contact: John K. Hart, Exec. Sec., AAOS, 430 N. Michigan Ave., Chicago 60611. (312) 822-0970.

March 10-14—Controversial Areas in Surgery. UCLA at El Mirador Hotel, Palm Springs. Wednesday-Sunday.

## Grand Rounds—Surgery

### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

### Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

### Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

## OF INTEREST TO ALL PHYSICIANS

### CMA Postgraduate Institutes and Circuit Courses

January 28-29—Southern Counties Regional Postgraduate Institute. CMA, UCI and Orange County Medical Society at El Mirador Hotel, Palm Springs. Thursday-Friday. Major Advances in Diagnostic Techniques, Rehabilitative Medicine, Youth and Drugs, Care of Seriously Injured. \$20. Contact: CMA.

February 15, 16, 17—March 8, 9, 10—Annual Postgraduate Circuit Courses—Spring Session. CMA and UCD at Mt. Shasta Community Hospital, Mt. Shasta; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn. \$20 for Spring Session. Contact: CMA.

March 4-5—West Coast Counties Regional Postgraduate Institute. CMA, UCSF and Monterey County Medical Society at Del Monte Lodge, Pebble Beach. Thursday-Friday. Contact: CMA.



- January 18-23—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. \$150. 50 hrs. Course to be repeated. Contact: Robert E. Rakel, M.D., Chairman, Family Practice Program, UCI. (714) 548-0651.
- January 21-22—**Sports Medicine.** USC at Century Plaza Hotel, Los Angeles. Thursday-Friday. \$95.
- January 22-23—**New and Old Antibiotics.** USC. Friday-Saturday. \$40.
- January 23-24—**Legal and Organizational Problems in Medical Practice: A Symposium for Medical Assistants.** UCSF. Saturday-Sunday.
- January 25-30—**Family Practice Refresher Course.** See January 18-23.
- January 30-31—**Ninth Annual Scientific Seminar—Memorial Hospital of Southern California.** Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Heartburn, Curable Hypertension, Abdominal Aorta Disorders, Medical Implications of Environmental Imbalance. \$15. Contact: June Weisbad, Medical Staff Sec., Memorial Hospital of Southern California, 3828 Hughes Avenue, Culver City 90231. (213) 836-7000.
- January 31—**Symposium—Immunologic Problems in Clinical Practice.** San Diego County Medical Society, Lederle Laboratories and American Academy of General Practice at El Cortez Hotel, San Diego. Sunday. Pathogenesis of Glomerulonephritis, chronic viral infections and auto-immune response, genetics and immunology, genetic counseling in OB practice, current status of tumor immunity, renal transplant, immunoglobulins and clinical significance of their determination, immunizations against infectious diseases. 5 hrs. Contact: Woodbury Perkins, M.D., Mercy Hospital, 4077 Fifth Ave., San Diego 92103. (714) 298-4141.
- February 1-12—**Family Practice.** USC. Two weeks. \$150.
- February 10-12—**Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital, San Francisco. Wednesday-Friday. Morning electives in Electrocardiography, Radiologic Demonstration of Common Problems of the Upper Gastrointestinal Tract, Clinical Workshops. Internal Medicine, Ob/Gyn, Treatment of Cancer, Psychiatry, Chest Disease, Surgical Specialties.
- February 19-25—**Loma Linda Postgraduate Assembly.** LLU Alumni Association at LLU and Ambassador Hotel, Los Angeles. Friday-Thursday. Cardiology, Ophthalmology, Dermatology, Pediatrics, Internal Medicine, Surgery, Neurology, Radiology, Business, Orthopedics, Plastic Surgery and Inhalation Therapy. \$50. 15 hrs. Contact: Paul H. Deeb, M.D., General Chairman, 1832 Michigan Ave., Los Angeles 90033. (213) 262-2173.
- February 22-24—**San Diego Biomedical Symposium—1971.** UCSD at Ramada Inn, Harbor Island, San Diego. Monday-Wednesday. Information processing and Instrumentation, New Developments from Industry Applicable to Hospital Environment, Data Storage and Retrieval, Instrumentation for Care of the Acutely Ill, Microprogrammed Minicomputers, Signal Conditioning and Preprocessing, Biomedical Applications of Simulation Techniques. Contact: R. D. Yoder, Dept. of Community Medicine, UCSD School of Medicine, University Hospital of San Diego County, 225 W. Dickinson St., San Diego 92103. (714) 291-3330.
- February 27-28—**Program at Franklin Hospital.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.
- March 7—**Personal Adjustments and Human Relations: Communication and Ethics: A Symposium for Medical Assistants.** UCSF. Sunday.
- March 12-19—**Marquette Medical Alumni Association.** Maui Hilton Hotel, Maui, Hawaii. One week. Contact: Robert H. Herzog, Marquette Medical Alumni Association, 561 N. 15th St., Milwaukee 53233.
- March 13-17—**California Medical Association—Annual Meeting.** Disneyland Hotel, Anaheim. Saturday-Wednesday.
- Continuously—**Basic Science Correlation in Disease.** VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.
- Continuously—**Ventura General Hospital Program.** UCI and Ventura General Hospital at Ventura General Hospital, Ventura. Monthly lectures by UCI faculty. January 16, Indications for Thyroid Surgery. Contact: UCI.
- Continuously—**Postgraduate Medical Lecture Series—Orange County.** UCI and Orange County Chapter, American Academy of General Practice at Saddleback Inn, Santa Ana. Monthly lectures by UCI faculty. January 11, Emergency Treatments of Facial Lacerations and Fractures; February 8, Emergency Aspects of Drug Intoxication; March 8, The Hyperactive Child. Contact: UCI.
- Continuously—**Postgraduate Medical Lecture Series—Riverside-San Bernardino.** UCI and Riverside-San Bernardino Chapter, American Academy of General Practice at Rams Horn Inn, San Bernardino. Monthly lectures by UCI faculty. January 21, Manipulative Therapy; February 18, Facts and Fantasies of Sensitivity Training. Contact: UCI.
- Continuously—**Dean's Day Program.** UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. January 28, Psychiatry; February 25, Pathology; March 25, Radiology; April 22, Community Medicine. Contact: UCSD.
- Continuously—**Biomedical Lecture Series.** UCSD. Third Wednesday monthly, 8:00 p.m., Basic Sciences Building, UCSD.
- Continuously—**Basic Science Lecture Series.** UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.
- Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General

Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

**Continuously—Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malpractice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MMN Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all Califor-

nia medical schools. Contact: Richard R. Getz, Exec. Dir., MMN, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

**Continuously—Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Practicing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Endocrinology-Metabolism, Gastroenterology, Hematology, Neurology, Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: February-March, April-May. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## TESTING FOR EARLY PITUITARY LESIONS

How do you test for small or early lesions of the pituitary gland?

"We test using the amino acid arginine, which is available for treatment of hepatic coma. It has very interesting properties in that it stimulates the release of growth hormone, which is the first thing to go in these lesions, and also of insulin. Normal subjects show a tenfold rise after the infusion. We give 30 grams over 30 minutes. It's well tolerated. At about 60 minutes one sees the peak level of growth hormone. For some reason that we don't understand, there is practically nothing that obese persons respond to. So if the patient is obese one has some difficulty. However, patients who are suspected of having panhypopituitarism usually are not obese so this is rarely a problem. In children 0.5 grams per kg is used and it works the same way."

—LOWELL L. SPARKS, M.D., San Francisco

Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# application for **HOTEL ACCOMMODATIONS**

## **ONE-HUNDREDTH** *Annual Session*

**CALIFORNIA MEDICAL ASSOCIATION • MARCH 13-17, 1971**

**ANAHEIM CONVENTION CENTER/DISNEYLAND HOTEL, ANAHEIM**

**SCIENTIFIC SESSIONS, ANAHEIM CONVENTION CENTER, BEGIN SATURDAY MORNING, MARCH 13**

**HOUSE OF DELEGATES OPENING SESSION, ANAHEIM CONVENTION CENTER, SATURDAY AFTERNOON, MARCH 13**

1. Fill in the form below *completely* for room accommodations at the CMA's 1971 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, except for suites, must be made through the Disneyland Hotel, 1441 S. West Street, Anaheim, California 92802, by February 12, 1971.
4. ALL SUITE RESERVATIONS MUST BE CLEARED THROUGH THE CMA CONVENTION OFFICE, SAN FRANCISCO. *IF YOU ARE REQUESTING A SUITE, DIRECT YOUR REQUESTS TO: CMA CONVENTION OFFICE, 693 SUTTER STREET, SAN FRANCISCO, CA 94102.*
5. CANCELLATIONS: Please notify Disneyland Hotel, 1441 S. West Street, Anaheim, of all cancellations.  
CHANGES: All other changes to be made directly with hotel at all times.
6. FIRST NIGHT DEPOSIT: PLEASE ENCLOSE THE FIRST NIGHT'S RENTAL AS DEPOSIT. REFUNDABLE ONLY IF HOTEL IS NOTIFIED 5 DAYS BEFORE ARRIVAL DATE.

### DISNEYLAND HOTEL

	Garden Rooms	Sierra Tower	Marina Tower
Singles	\$ 15	\$17-20	\$ 24
Twins or doubles	\$ 19	\$21-24	\$ 28
Additional person in room	\$ 4	\$ 4	\$ 4
1 Bedroom suites		\$ 65	\$ 85
2 Bedroom suites		\$ 90	\$110

### GRAND HOTEL

Singles	\$ 16
Twins or doubles	\$ 22
Triples	\$ 26
1 Bedroom suites	\$ 56
2 Bedroom suites	\$ 72

**SEND TO: DISNEYLAND HOTEL RESERVATIONS**

1441 S. West Street, Anaheim, California 92802

Please reserve the following accommodations for the CMA's 1971 Annual Session in Anaheim, March 13-17.

Single Bedroom \$. . . . .Twin-Bedded \$. . . . .Double Bed \$. . . . .Suite \$. . . . .  
 First Choice Hotel . . . . . Second . . . . .  
 Arrival (date) . . . . . Hour . . . . . a.m. Departure (date) . . . . . Hour . . . . . a.m.  
 . . . . . p.m. . . . . p.m.

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: . . . . . Officer? . . . . Delegate? . . . . Alternate? . . . . Speaker? . . . .

Address: . . . . . County . . . . .

City and State . . . . . Zip Code . . . . .

GUESTS' NAMES AND ADDRESSES:

. . . . .  
 . . . . .  
 . . . . .

# 100th Annual Session Program

Anaheim Convention Center  
March 13 to 17, 1971



- Scientific Sessions
- Motion Picture Symposia
- Scientific and Technical Exhibits
- Meetings of the House of Delegates

## California Medical Association



**CALIFORNIA MEDICAL ASSOCIATION 100th ANNUAL SCIENTIFIC ASSEMBLY**  
**March 13-17, 1971 - Anaheim Convention Center**  
**DAILY SCHEDULE**

SATURDAY, MARCH 13			
Section Meetings:	Room	Morning	Afternoon
General Practice and Orthopedics	Santa Ana #2	9:00	
Internal Medicine	Orange #9-#10, Costa Mesa #11	9:00	
Orthopedics and General Practice	Santa Ana #2	9:00	
Pathology	Fullerton #7 and #8	9:00	
Special Conferences:			
Effective Medical Writing: Seminar/Workshop	Costa Mesa #12		8:30
American College of Chest Physicians	Westminster #16 and #17		9:00
Congress on Health of the School-Age Child	Santa Ana #1		9:00
Audio-Digest Foundation	Lounge, adj. to Santa Ana		9:00
Medical Media Network	North Lobby		9:00
Live Teaching Clinics	Arena, adj. to Tech. Exhibits	9:00/11:00	
Radiology Conference	Orange County #21		9:30
Fifth Annual Cancer Symposium	Garden Grove #3		2:00
Hospital Directors of Respiratory Therapy	Orange #9 and #10		2:00
General Meeting:			
Psychiatric Focus on Medical and Social Change	Santa Ana #2		2:00
CMA HOUSE OF DELEGATES—Opening Session	Anaheim		4:00
Motion Picture Symposium	Orange County #22		2:00
Scientific and Organizational Exhibits	Grand Lobby		9:00
SUNDAY, MARCH 14			
Section Meetings:			
Allergy	Garden Grove #4		9:00
Anesthesiology	Huntington Beach #6		9:30
Dermatology	Westminster #16	8:30	
General Practice and Orthopedics	Santa Ana #2	9:00	
Internal Medicine	Orange #9-#10, Costa Mesa #11	9:00	
Ophthalmology	Westminster #16 and #17		1:30
Orthopedics and General Practice	Santa Ana #2	9:00	
Otolaryngology	Costa Mesa #12	9:30	
Physical Medicine and Rehabilitation	Westminster #17	9:00	
Plastic Surgery	Fullerton #7 and #8		9:00
Radiology	Orange County #21	9:00	
Special Conferences:			
Congress on Health of the School-Age Child	Santa Ana #1		9:00
Audio-Digest Foundation	Lounge, adj. to Santa Ana		9:00
Medical Media Network	North Lobby		9:00
Live Teaching Clinics	Arena, adj. to Tech. Exhibits	9:00/11:00	
Pathology Conference	Garden Grove #3		9:00
L. Henry Carland Memorial Lecture	Orange County #21		2:00

SUNDAY, MARCH 14 (Continued)				
General Meeting:		Room	Morning	Afternoon
Environmental Activism—A Positive Approach		Santa Ana #2		2:00
Motion Picture Symposium		Orange County #22		2:00
Scientific and Organizational Exhibits		Grand Lobby		9:00
MONDAY, MARCH 15				
Section Meetings:				
General Surgery				
Internal Medicine		Fullerton #7 and #8		12:00
Obstetrics and Gynecology		Orange #9-#10, Costa Mesa #11	9:00	
Pediatrics		Garden Grove #4		8:30
Psychiatry and Neurology		Garden Grove #3		9:00
Psychiatry and Neurology/Obstetrics and Gynecology		Westminster #16 and #17	9:00	
Psychiatry and Neurology		Garden Grove #4		1:30
Urology		Westminster #16 and #17		3:10
Huntington Beach #6				9:00
Special Conferences:				
Audio-Digest Foundation		Lounge, adj. to Santa Ana		9:00
Medical Media Network		North Lobby		9:00
Live Teaching Clinics		Arena, adj. to Tech. Exhibits	9:00/11:00	
Emergency and Disaster Care Symposium		Santa Ana #1		9:00
Patient Education		Santa Ana #2	9:00	
Multiphasic Screenings: Help or Hindrance?		Costa Mesa #12	9:00	
Evaluating the Quality of Medical Care		Costa Mesa #11 and #12		2:00
How to Help Your Patients Quit Smoking		Orange #9 and #10		2:00
General Meeting:				
Your Continuing Education—Voluntary or Involuntary?		Santa Ana #2		1:30
Motion Picture Symposium		Orange County #22		1:30
Scientific and Organizational Exhibits		Grand Lobby		9:00
TUESDAY, MARCH 16				
Section Meetings:				
Industrial Medicine and Surgery				
Preventive Medicine and Public Health		Huntington Beach #6	9:30	
		Garden Grove #3	9:00	
Special Conferences:				
Audio-Digest Foundation		Lounge, adj. to Santa Ana		9:00
Medical Media Network		North Lobby		9:00
The Physician's Assistant in California		Santa Ana #2	9:00	
Symposium on Epilepsy		Santa Ana #1		9:00
Heart and Exercise		Westminster #16 and #17		9:00
Adolescent Sensuality		Costa Mesa #11	9:00	
The Physician and the Legislative Process		Fullerton #7 and #8	9:30	
Gastroenterology		Santa Ana #2		2:00
Anaheim				1:30
Grand Lobby				9:00
CMA HOUSE OF DELEGATES				
Scientific and Organizational Exhibits				
WEDNESDAY, MARCH 17				
CMA HOUSE OF DELEGATES				
		Anaheim	9:00 to conclusion of business	



# Scientific Program

## 100th Annual Session

### CALIFORNIA MEDICAL ASSOCIATION

### Anaheim Convention Center

**March 13-17, 1971**

HOUSE OF DELEGATES  
OPENING MEETING  
SATURDAY, MARCH 13  
4:00 P.M.

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# CALIFORNIA MEDICAL ASSOCIATION



**RALPH W. BURNETT**, *President*



**ROBERTA F. FENLON**, *President-Elect*



# Information

## BADGES:

It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

## COUNCIL:

The Council will meet Friday, March 12, 4:00 p.m., and Saturday, March 13, 9:00 a.m. to noon. Rooms will be posted on the hotel schedule boards.

## HOUSE OF DELEGATES:

For the list of delegates and alternates, meeting times, places, and agenda—see pages 35 to 40.

## EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(714) 635-8440. From 9:00 a.m. to 5:00 p.m., Saturday, March 13 through Wednesday, March 17.

## MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company—(714) 635-8440.

*Location:* South Lobby, Anaheim Convention Center.

*Hours:* 9:00 a.m. to 5:00 p.m.

The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the Convention number.

*Routine Messages:* Will be kept at the Message Center in the South Lobby, Anaheim Convention Center.

Physicians are *requested* to *check with the Message Center at least once a day.*

## INDEX TO PARTICIPANTS:

See pages 7 to 11.

## TECHNICAL EXHIBITS:

Arena and Grand Lobby, Anaheim Convention Center.

## MOTION PICTURE SYMPOSIA:

Will be shown in Orange County Room #22. See page 28.

## SCIENTIFIC AND ORGANIZATIONAL EXHIBITS:

Grand Lobby, Anaheim Convention Center. See page 30.

## REGISTRATION AND INFORMATION:

Registration and information desks are located at the *Main Entrance to the Arena*. All members, guests and visitors are requested to register immediately on arrival. There is no charge for registration.

Desks are open Saturday through Wednesday.

Admission to the general and section meetings and exhibit areas is by badge only.

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

## QUALIFICATIONS/REQUIREMENTS

### FOR REGISTRATION:

All *M.D.s* with credentials showing that they hold valid license to practice medicine. (Membership card: C.M.A. county medical society/association; AMA.)

*Medical students* upon presentation of credentials from the medical schools. (Membership card, Student Medical Association, or letter from Dean's office.)

*Medical Assistants* upon presentation of a letter from the physician-employer or C.M.A.A. membership card.

*Military paramedical personnel* upon presentation of a letter requesting their admittance, written by their commanding officer.

*Dentists (D.D.S.)—Doctors of Veterinary medicine (D.V.M.)—registered nurses (R.N.)—student nurses—x-ray technicians—laboratory technicians—allied public health personnel—others* will be admitted provided they have proper identification.

**ALL QUESTIONS ON ADMISSION** will be passed upon by member of the Committee on Registration present at the desk.

# Guest Speakers

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## GENERAL MEETINGS

*Saturday, March 13*

*2:00 p.m.—Santa Ana #2*

### Psychiatric Focus on Medical and Social Change

- Milton M. Miller, M.D., Professor and Chairman  
Department of Psychiatry, University of Wisconsin  
Medical School, Madison
  - Howard P. Rome, M.D., Chief, Department of Psy-  
chiatry, Mayo Clinic, Rochester
- 

*Sunday, March 14*

*2:00 p.m.—Santa Ana #2*

### Environmental Activism—A Positive Approach

- Mr. Lewis H. Butler, Assistant Secretary for Plan-  
ning and Evaluation, Department of Health, Edu-  
cation, and Welfare, Washington, D.C.
  - Paul N. McCloskey, Congressman, 11th Congres-  
sional District (San Mateo County), Washington, D.C.
- 

*Monday, March 15*

*1:30 p.m.—Santa Ana #2*

### Your Continuing Medical Education—Voluntary or Involuntary?

- Clement R. Brown, Jr., M.D., Director of Medical  
Education, Chestnut Hill Hospital, Philadelphia
- George E. Miller, M.D., Director of Research in Med-  
ical Education, University of Illinois College of Med-  
icine, Chicago



# Out - of - State Guests

## SECTIONS and SPECIAL CONFERENCES

- *General Practice/Orthopedics*

James Harry Cyriax, M.D., Consultant, Orthopaedic Physician, St. Thomas's Hospital, London

- *General Surgery*

James D. Hardy, M.D., Professor and Chairman, Department of Surgery, University of Mississippi School of Medicine, Jackson

- *Ophthalmology*

Matthew Davis, M.D., Department of Ophthalmology, University of Wisconsin School of Medicine, Madison

Paul C. Wetzig, M.D., University of Colorado School of Medicine, Denver

- *Otolaryngology*

Muhammed H. Saffouri, M.D., Visiting Professor, Head and Neck Surgery, UCLA; Chairman, Department of Otorhinolaryngology, University of Kuwait, Persian Gulf

Erwin Rock, M.D., Assistant Clinical Professor of Otolaryngology, Albert Einstein College of Medicine, Bronx

Abe Schulman, M.D., Assistant Clinical Professor of Otolaryngology, Albert Einstein College of Medicine, Bronx

Bernard Seife, M.D., Associate Professor of Otolaryngology, Albert Einstein College of Medicine, Bronx

- *Pathology*

C. D. West, M.D., Professor of Medicine, University of Utah College of Medicine, Salt Lake City

- *Physical Medicine and Rehabilitation*

Michael Fearnley, M.D., Hamilton, Ontario

Michael T. Carpendale, M.D., Medical Director, New York State Rehabilitation Hospital, West Haverstraw

- *American College of Chest Physicians, California Chapter, Annual Meeting*

Donald B. Effler, M.D., Chief, Thoracic Surgical Section, Cleveland Clinic; President, The Society of Thoracic Surgeons, Cleveland

- *Fifth Annual Cancer Symposium*

M. Vera Peters, M.D., Senior Radiotherapist, Ontario Cancer Institute, incorporating The Princess Margaret Hospital; Assistant Professor of Therapeutic Radiology, University of Toronto Faculty of Medicine, Toronto

- *Physician's Assistant in California*

Richard A. Smith, M.D., Director, MEDEX Program, State of Washington, University of Washington School of Medicine, Seattle

- *Seminar/Workshop on Medical Writing*

Charles G. Roland, M.D., Past President, American Medical Writers Association; Chairman, Department of Publications and the Medical Library, Mayo Clinic, Rochester

- *Symposium on Epilepsy*

David B. Clark, M.D., Professor and Chairman, Department of Neurology, University of Kentucky Medical Center, Lexington

David Daly, M.D., Professor and Chairman, Department of Neurology, University of Texas, Southwestern Medical School at Dallas

Richard Masland, M.D., Director, New York Neurological Institute; Professor and Chairman, Department of Neurology, Columbia University College of Physicians and Surgeons, New York City

A. Earl Walker, M.D., Professor and Chairman, Department of Neurology, Johns Hopkins University School of Medicine; Neurosurgeon-in-Charge, Johns Hopkins Hospital, Baltimore

Philip T. White, M.D., Professor and Chairman, Division of Neurology, Medical College of Wisconsin (formerly Marquette School of Medicine), Milwaukee

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## To Register — You MUST have proper identification

### QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION:

*All M.D.s* with credentials showing that they hold valid license to practice medicine. (Membership card: CMA; county medical society/association; AMA.)

*Medical students* upon presentation of credentials from their medical schools. (Membership card, Student Medical Association, or letter from Dean's office.)

*Medical Assistants* upon presentation of a letter from the physician-employer or C.M.A.A. membership card.

*Military paramedical personnel* upon presentation of a letter requesting their admittance, written by their commanding officer.

*Dentists (D.D.S.)—Doctors of Veterinary medicine (D.V.M.)—registered nurses (R.N.)—student nurses—x-ray technicians—laboratory technicians—allied public health personnel—and others* will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

## You may be reached through (714) 635-8440

### EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(714) 635-8440.

From 9:00 a.m. to 5:00 p.m., Saturday, March 13 through Wednesday, March 17.

### MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company—(714) 635-8440.

*Location:* South Lobby, Anaheim Convention Center.

*Hours:* 9:00 a.m. to 5:00 p.m.

The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the Convention number.

*Routine Messages:* Will be kept at the Message Center in the South Lobby, Anaheim Convention Center.

Physicians are *requested to check with the Message Center at least once a day.*



# Special Conferences

SATURDAY, MARCH 13

8:30 a.m.—Costa Mesa #12

## SEMINAR/WORKSHOP ON EFFECTIVE MEDICAL WRITING

*Sponsored by the Pacific Southwest Chapter and the Northern California Chapter of the American Medical Writers Association*

This seminar and workshop is planned to assist physicians, editors and others engaged in medical writing to communicate scientific information in an accurate, lucid and readable style. The emphasis will be on the "nuts and bolts" aspects of medical writing—to develop the craft, out of which comes the art of writing.

To receive maximum benefit from the course, each participant is urged to bring (or to submit in advance) a manuscript currently in preparation or recently published. Possible methods of improving these manuscripts will be discussed, in consultation with the faculty, during small-group workshop sessions.

**Enrollment:** The registration fee is \$30.00 (\$25.00 for AMWA members), including luncheon. Additional guest luncheon reservations are available at \$6.00 per person. Enrollment is limited, so please register by mail in advance. Make checks payable to AMWA-Pacific Southwest Chapter and send to: Miss Frances Larson, Treasurer, AMWA, 4583 Ambrose Avenue, Los Angeles 90027.

If possible, please submit a manuscript for discussion with the application, so that copies can be made for all participants in your discussion group. Please also indicate your area of interest in medical or scientific writing, so that you will be grouped with those who can provide maximum assistance in your field.

8:30—Registration

9:00—Welcoming remarks

9:15—The Fight Against Word Pollution—Charles G. Roland, M.D., Rochester, Minn., by invitation

9:45—Questions and Discussion

10:00—Recess—Coffee and rolls will be served

10:15—Workshop I—Titles and first paragraph

11:15—Workshop II—Organization of paper or research report

## LUNCHEON

12:30—Room to be Assigned

1:15—Luncheon Address: Adventures in Medical Writing—Chauncey D. Leake, Ph.D., San Francisco, by invitation

2:00 p.m.—Costa Mesa #12

2:00—The Ecology of a Medical Manuscript—Malcolm S. M. Watts, M.D., San Francisco

2:30—Questions and Discussion

2:45—Recess—Coffee will be served

3:00—Workshop III—Summary and references

4:00—General discussion and summation

SATURDAY, MARCH 13

9:00 a.m.  
—Westminster #16 and #17

## AMERICAN COLLEGE OF CHEST PHYSICIANS, CALIFORNIA CHAPTER

Annual Meeting

*Two scientific sessions of the ACCP Annual Meeting will take place simultaneously in adjoining meeting rooms, and all physicians are cordially invited to attend.*

8:30—Registration

Westminster #16

## Medical—Cardiac Diseases

Chairman: George C. Griffith, M.D., La Canada

9:00—Nature of Coronary Circulation in Health and Disease—Richard J. Bing, M.D., Pasadena

9:20—Discussion—William Ganz, M.D., Los Angeles, by invitation

9:30—Evaluation of Newer Anti-Anginal Drugs—Travis Winsor, M.D., Los Angeles

9:50—Discussion—Herbert Gold, M.D., Beverly Hills

10:00—Circulatory Assist for Myocardial Shock—Eliot Corday, M.D., Beverly Hills

10:20—Discussion—Alfred Goldman, M.D., Los Angeles

10:30—Recess

10:40—Clinical Application of Transthoracic Electrical Impedance—Joseph M. Van De Water, M.D., Duarte, by invitation

10:55—Discussion—Harold L. Karpman, M.D., Los Angeles

11:00—Joint Medical-Surgical Session

Westminster #16 and #17

9:00—

Westminster #17

### **Surgery—Thoracic Diseases**

Chairman: Elmer C. Rigby, M.D., Los Angeles

9:00—Lung Transplantation—John R. Benfield, M.D., Torrance

9:20—Discussion—Karlman Wasserman, M.D., Torrance, by invitation

9:30—Endoscopy: Past, Present and Future—George Berci, M.D., Los Angeles, by invitation

9:50—Discussion—H. Brodie Stephens, M.D., San Francisco

10:00—Surgical Experience in the Management of Myasthenia Gravis—Donald G. Mulder, M.D., Los Angeles

10:20—Discussion—Christian Herrmann, Jr., M.D., Los Angeles, by invitation

10:30—Recess

10:40—The Traumatic Chest—Lyman A. Brewer, III, M.D., Los Angeles

1:00—Joint Medical-Surgical Session

Westminster #16 and #17

SATURDAY, MARCH 13

Westminster #16 and #17

1:00— **Joint Medical—Surgical Session**

Chairman: David J. Dugan, M.D., Oakland  
Case Presentations

Interstitial Lung Diseases—Ralph C. Jung, M.D., Los Angeles

Chest Pain—John G. Mohler, M.D., Los Angeles

Refractory Angina—Steven B. Rubins, M.D., Beverly Hills  
Tumor of the Lung—Mitchell Tarkoff, M.D., Oakland

Prophylactic Tuberculosis—James M. Kieran, M.D., Berkeley

SATURDAY, MARCH 13 12:00 noon—Room to be Assigned

12:00—Luncheon Meeting of the American College of Chest Physicians, California Chapter

Chairman: Angelo M. May, M.D., San Francisco  
Business Meeting and Election of Officers  
Presentation of "Man-of-the-Year" Award

Honorary Lecture: Revascularization of the Heart—Donald B. Effler, M.D., Cleveland, by invitation

SATURDAY, MARCH 13

Westminster #16

### **Medical—Thoracic Diseases**

Chairman: Marvin S. Harris, M.D., Los Angeles

2:00—Obstructive Lung Diseases—Oscar J. Balchum, M.D., Los Angeles, by invitation

2:20—Discussion—Wilbur Y. Hallett, M.D., Los Angeles

2:30—Pulmonary Lavage—Karlman Wasserman, M.D., Torrance, by invitation

2:50—Discussion—John R. Benfield, M.D., Torrance

3:00—Metabolic Aspects of Thoracic Neoplasms and Other Diseases of the Chest—Charles R. Kleeman, M.D., Los Angeles

3:20—Discussion—Orville F. Grimes, M.D., San Francisco

3:30—Recess

3:40—Pulmonary Dysfunction Associated with Myocardial Infarction—Steven E. Levy, M.D., Los Angeles, by invitation

4:00—Discussion—William W. Parmley, M.D., Los Angeles, by invitation

4:10—Fungus Diseases—Hans E. Einstein, M.D., Bakersfield

4:30—Discussion—David Salkin, M.D., San Fernando, by invitation

SATURDAY, MARCH 13

Westminster #17

### **Surgery—Cardiac Diseases**

Chairman: Angelo M. May, M.D., San Francisco

2:00—Current Assessment of Cardiac Transplantation—Richard J. Cleveland, M.D., Torrance, by invitation

2:20—Discussion—Albert A. Kattus, M.D., Los Angeles

2:30—Follow-up Studies of Patients Treated by Revascularization—Donald B. Effler, M.D., Cleveland, by invitation

3:00—Surgery for Complications of Myocardial Infarction—Jack M. Matloff, M.D., Los Angeles, by invitation

3:20—Discussion—Donald G. Mulder, M.D., Los Angeles

3:30—Recess

3:40—Prosthetic Valve Surgery—John E. Connolly, M.D., Irvine

4:00—Tissue Valve Surgery—Benson B. Roe, M.D., San Francisco

4:20—Discussion—William W. Angell, M.D., Palo Alto, by invitation

4:30—Surgical Treatment of Congenital Heart Disease—Bertrand W. Meyer, M.D., Los Angeles

4:50—Discussion—George C. Lindesmith, M.D., Los Angeles



SATURDAY, MARCH 13  
SUNDAY, MARCH 14

9:00 a.m.—Santa Ana #1

## CONGRESS ON HEALTH OF THE SCHOOL-AGE CHILD

*California Medical Association  
Committee on School and College Health*

### Symposium on School Health: Look to the '70's

Chairman: Harriett Randall, M.D., Glendale

9:00—Introductory Remarks

9:05—Are School Nurses Busy?—Lillian Cassidy, M.A., P.H.N.,  
Los Angeles, by invitation

9:15—The Board Member and the Doctor in School Health—  
Donald D. Newman, M.D., Los Angeles

9:30—Can We Educate for Health?—Ruth Rich, Ed.D., Los An-  
geles, by invitation

9:40—Questions and Answers Session

9:45—Implementing the Framework for Health Instruction

*California Medical Association Committee on  
School and College Health*

#### PANEL DISCUSSION

Members of the Panel: John T. Foder, Ed.D., San Fernando, by  
invitation; Ben C. Gmur, Ed.D., Los Angeles, by invita-  
tion; Wilfred C. Sutton, Ed.D., San Fernando, by invita-  
tion

10:30—Questions and Answers Session

11:00—Recess

11:15—Comprehensive Health Planning and School Health

*Sponsored by the Maternal and Child Health Program, UC  
Berkeley School of Public Health, and Bureau of  
Maternal and Child Health, State Department  
of Public Health*

#### PANEL DISCUSSION

Members of the Panel: Otis Cobb, M.D., Woodland; Victor Eis-  
ner, M.D., Berkeley; Frederick B. Hodges, M.D., Berke-  
ley; Marsden G. Wagner, M.D., Los Angeles, by invita-  
tion

12:15—Questions and Answers Session

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2:00—Symposium on Dyslexia

*California Medical Association Committee on  
School and College Health*

Moderator: Byron Demorest, M.D., Sacramento

2:00—Dyslexia: Fact or Fiction?—Henry Bamman, Ph.D., Sac-  
ramento, by invitation

Psychiatric Evaluation of Children With Reading Prob-  
lems—Gerald Jampolsky, M.D., Tiburon

The Role of Eye Care in Dyslexia—Byron Demorest,  
M.D., Sacramento

Identification and Treatment of Dyslexic Children—Helen  
Cofman, M.D., San Francisco, by invitation

3:15—State College and Community College Health Service  
Crisis

#### SYMPOSIUM

Co-Chairmen: William Wanamaker, M.D., Beverly Hills;  
William H. Wickett, Jr., M.D., Fullerton

4:15—Questions and Answers Session

4:30—Progress Report on the California State Drug Education  
Training Program

*Sponsored by the State Department of Education and the  
State Office of Narcotics and Drug Abuse Coordination*

Participants: Donald A. McCune, Sacramento, by invitation;  
Ruth Thomas, Visalia, by invitation; Arthur Suddjian,  
Sacramento, by invitation

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SUNDAY, MARCH 14

9:00 a.m.—Santa Ana #1

9:00—VD: The Avoidable Epidemic

*California Medical Association Subcommittee  
on Venereal Disease*

#### SYMPOSIUM

Chairman: Horace F. Sharrocks, M.D., Sebastopol

10:00—Postmortem on Sex Education in Anaheim: What Went  
Wrong?

*California School Nurses Organization and California Medical  
Association Committee on School and College Health*

Participants: Tom W. Robinson, M.D., Newport Beach; James  
C. Voss, Jr., Santa Rosa, by invitation; Sally R. Wil-  
liams, R.N., Garden Grove, by invitation

11:15—Questions and Answers Sessions

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1:00—Involving Youth in Decision Making

*Sponsored by the California Council on Children and Youth*

Moderator: Mrs. Robert T. Adams, Lafayette, by invitation

2:00—Looking at Children's Emotional Health

*Sponsored by the California Congress of Parents and Teachers*

Moderator: Mrs. Kenneth Smith, Santa Ana, by invitation

#### PANEL DISCUSSION

Members of the Panel: Irving H. Berkovitz, M.D., Beverly Hills;  
Jean E. A. Neighbor, M.D., Walnut Creek; Mrs. Kenneth  
Smith, Santa Ana, by invitation; Mrs. William Saylor,  
South Laguna, Orange, by invitation

3:00—What's Going on in the Kindergarten?

*Sponsored by the California School Health Association*

#### SYMPOSIUM

Moderator: Mrs. Doris Bell, Vallejo, by invitation

4:00—The Medical Aspects of Physical Fitness

*California Medical Association Committee on  
the Medical Aspects of Sports*

#### SYMPOSIUM

Moderator: Philip H. McFarland, M.D., Fullerton

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5:00—Annual Meeting of the California School Health Associa-  
tion (Southern Section)

Chairman: Seymour Eiseman, Dr. P.H., San Fernando, by in-  
vitation

SATURDAY, MARCH 13 9:00 a.m. to 5:00 p.m. Daily  
SUNDAY, MARCH 14 —Lounge, adjacent to  
MONDAY, MARCH 15 Santa Ana Rooms  
TUESDAY, MARCH 16

### AUDIO-DIGEST FOUNDATION

(a Non-Profit Subsidiary of California Medical Association)

Audit at your leisure a wide selection of the tape-recorded summaries of leading national meetings and authoritative surveys of current literature provided by Audio-Digest. Catalog of available material will be provided in the Lounge.

Coordinator: Claron L. Oakley, Los Angeles, by invitation

SATURDAY, MARCH 13 9:00 a.m. to 5:00 p.m. Daily  
SUNDAY, MARCH 14 —North Lobby  
MONDAY, MARCH 15  
TUESDAY, MARCH 16

### MEDICAL MEDIA NETWORK

Physicians are invited to view their choice of a wide variety of 8 mm. cartridge educational films. Study guides and other supporting materials will be available.

Coordinator: Richard R. Getz, Los Angeles, by invitation

SATURDAY, MARCH 13 Twice Daily at 9:00 a.m. and  
SUNDAY, MARCH 14 11:00 a.m.—Arena Seating,  
MONDAY, MARCH 15 adjacent to the Technical Exhibits

### LIVE TEACHING CLINICS

Presentation of cases, with physicians and patients—live, and on closed-circuit television—will be conducted by invited speakers. Audience participation is invited.

Coordinator: Robert J. Thompson, West Point, Pa., by invitation

SATURDAY, MARCH 13 9:30 a.m.—Orange County #21

### RADIOLOGY CONFERENCE

Committee on Cancer, California Medical Association

9:30 a.m. to 12:00 noon—THERAPY SESSION

Discussion of Testicular Tumors

Moderator: R. Wilbur Melbye, M.D., Los Angeles

9:30—Pathology—Nancy E. Warner, M.D., Los Angeles, by invitation

9:55—Clinical Behavior—Samuel S. Kurohara, M.D., Los Angeles

10:20—Chemotherapy—J. S. Bonorris, M.D., Los Angeles

10:45—Radiation Therapy—Frederick W. George III, M.D., Los Angeles

11:00—Surgery—Stanley A. Brosman, M.D., Torrance  
11:20—Questions and Answers Session  
Moderator: R. Wilbur Melbye, M.D., Los Angeles

1:30 p.m. to 3:30 p.m.—DIAGNOSTIC SESSION

Coordinator: D. E. Blickenstaff, M.D., La Jolla

SATURDAY, MARCH 13 2:00 p.m.—Garden Grove #3

### FIFTH ANNUAL CANCER SYMPOSIUM

*Sponsored Jointly by the California Medical Association, the California Division and the Orange County Branch of the American Cancer Society*

#### LYMPHOMA AND SOFT TISSUE SARCOMA: THE SWORD, THE RAY, AND THE ELIXIR

Chairman: Melvin A. Shiffman, M.D., Anaheim

2:00—Welcome—Melvin A. Shiffman, M.D., Anaheim, First Vice-President, Orange County Branch, American Cancer Society

#### LYMPHOMA:

2:05—The Ray—M. Vera Peters, M.D., Toronto, by invitation

2:20—The Elixir—Saul A. Rosenberg, M.D., Stanford, by invitation

2:35—The Sword—Ralph L. Byron, Jr., M.D., Duarte

2:50—Questions and Answers Session

3:10—Recess—Coffee will be served

#### SARCOMA:

3:25—The Sword—Ralph L. Byron, Jr., M.D., Duarte

3:40—The Ray—M. Vera Peters, M.D., Toronto, by invitation

3:55—The Elixir—Saul A. Rosenberg, M.D., Stanford, by invitation

4:10—Questions and Answers Session

SUNDAY, MARCH 14 9:00 a.m.—Garden Grove #3

### PATHOLOGY CONFERENCE

*Sponsored by the American Cancer Society, California Division; the California Medical Association Committee on Cancer; Member Pathologists, Los Angeles County-USC Medical Center*

Central Nervous System and Spinal Cord Tumors

Moderator: Richard M. Davis, M.D., Los Angeles

Participants: Clark Fobes, M.D., San Bernardino, by invitation; Roger Terry, M.D., Los Angeles, by invitation

9:00 a.m. to 12:30 p.m.

2:00 p.m. to 5:30 p.m.

The registration fee for this Conference is \$30.00, which includes attendance, a set of 25 slides, protocol and agenda. For attendance only, the fee is \$15.00. There is no charge for residents and interns. Those wishing to attend are requested to register with Weldon K. Bullock, M.D., Executive Director, Tumor Tissue Registry, Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033.



SUNDAY, MARCH 14

2:00 p.m.—Orange County #21

**Fifth Annual  
L. HENRY GARLAND  
MEMORIAL LECTURE**

*Sponsored by the California Radiological Society*

2:00—Introduction—Charles G. Campbell, M.D., La Jolla

2:05—New Approaches to the Analysis of Cancer Data—Antolin Raventos, M.D., Davis, by invitation

3:00—Recess

3:15—Annual Meeting—California Radiological Society

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MONDAY, MARCH 15

9:00 a.m.—Santa Ana #1

**EMERGENCY and DISASTER  
PREPAREDNESS**

*Symposium*

*Commission on Community Health Services, Committee on  
Automotive and Traffic Safety, Committee on Disaster  
Medical Care, Committee on Emergency Medical Care  
of the California Medical Association*

Program Coordinator: Emile L. Meine, M.D., Panorama City

Moderators: Wayne P. Chesbro, M.D., Berkeley;

Thomas W. Lyons, M.D., La Mesa

9:00—Fire Disasters

- Initial Care and Transportation of Severe Burn Cases
- Types and Emergency Treatment of Fire and Smoke Casualties
- Medical Preplanning for Major Fires
- Case Study

Earthquake Disasters

- Report on Peruvian Earthquake
- Prognosis for California

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12:00—Lunch recess

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2:00—Aviation Safety

- Emergency Medical Care in Aviation Disasters
- Medical Preplanning at Major Airports
- Coordination of Hospital Services in Areas Adjacent to Major Airports
- Specialized Medical Training for Aircraft Disasters

4:00—Emergency Ambulance Service: Film

- Transportation of Injured

**16 ONE HUNDREDTH ANNUAL SESSION**

MONDAY, MARCH 15

9:00 a.m.—Santa Ana #2

**PATIENT EDUCATION**

*Sponsored by the Society for Public Health Education, Inc.*

**ROUND TABLE DISCUSSIONS**

Specialists in patient education and discussion leaders will present case material and offer consultation on educational methods.

Participants: All by invitation

Don Britt, M.P.H., Berkeley, Coordinator, Doctoral Research Program, Division of Health Education, UC Berkeley School of Public Health

Marguerite De La Vega, M.P.H., Oakland, Education Director, Planned Parenthood, Alameda and San Francisco Counties

Mayhew Derryberry, Ph.D., Berkeley, Lecturer, Health Education Programs, UC Berkeley School of Public Health

Lloyd Frost, M.P.H., San Francisco, Director, San Francisco Comprehensive Health Planning Council

Eli Glogow, Dr. P.H., Los Angeles, Associate Professor, School of Public Administration, USC

Dan Hampshire, M.H.A., San Francisco, Coordinator, Department of Continuing Education, Pacific Medical Center

Laura Keranen, M.P.H., Oakland, Health Educator, Kaiser Permanente Medical Center

Sarah Mazelis, M.P.H., San Francisco, Educator-Evaluator, Regional Medical Programs, Area I

Catherine Vavra, M.P.H., Los Angeles, Senior Health Educator, Los Angeles County Health Department

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MONDAY, MARCH 15

9:00 a.m.—Costa Mesa #12

**Multiphasic Screening: Help or Hindrance?**

*California Medical Association Committee on  
Occupational Health*

Moderator: Robert S. Hockwald, M.D., San Francisco  
Topics and speakers to be announced

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MONDAY, MARCH 15 2:00 p.m.—Costa Mesa #11 and #12

**EVALUATING THE QUALITY OF  
MEDICAL CARE IN CALIFORNIA**

*California Medical Association Medical Staff  
Survey Committee*

2:00—How do CMA's Medical Staff Survey Teams Evaluate the Quality of Acute Care Services in Hospitals?—Bert L. Halter, M.D., San Francisco, Chairman, Medical Staff Survey Committee

2:20—How is the Medical Staff Survey Program Relevant to State Licensure and Certification of Hospitals?—Speaker from the State Department of Public Health to be announced

2:30—How is the Medical Staff Survey Program Relevant to Medicare?—Mercia Kahn, San Francisco, Regional Representative, Bureau of Health Insurance, Social Security Administration, Department of Health, Education, and Welfare, by invitation

2:50—Recess

3:10—How is the Medical Staff Survey Program Relevant to Hospital Accreditation?—Speaker from the Joint Commission on Accreditation of Hospitals to be announced

3:30—How is the Medical Staff Survey Program Relevant to the California Hospital Association and its Members?—Speaker from the California Hospital Association to be announced

3:50—How does the Medical Staff Survey Program Relate to the Legal Duty of the Governing Board, the Administration, and the Medical Staff to Maintain a High Standard of Medical Care?—Speaker to be announced

4:10—Whither Long-Term Care Review?—Pierre Salmon, M.D., San Mateo, Chairman, Committee on Long-Term Care Review

4:30—How is an Evaluation Program Organized and Administered?—Parkes A. Harris, San Francisco, Coordinator, Medical Staff Survey Program, by invitation

4:50—Open to questions from the floor

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MONDAY, MARCH 15      2:00 p.m.—Orange #9 and #10

### HOW TO HELP YOUR PATIENTS QUIT SMOKING

*Sponsored by the California Interagency Council on  
Smoking and Health*

Diagnostic Counseling and Treatment Approaches for Smoking  
Cessation in Office and Hospital Situations

Moderator: Gerald Hill, M.D., San Rafael

2:00—Round Table Discussants:

Stewart Dadmun, M.D., San Diego  
George Saunders, M.P.H., San Francisco, by invitation  
Maxwell R. Rosenblatt, M.D., Los Angeles  
Jack Liebman, M.D., San Francisco, by invitation  
John Callaghan, M.D., Redwood City  
Elfrieda Fasal, M.D., Berkeley, by invitation  
Homer D. Peabody, Jr., M.D., San Diego

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TUESDAY, MARCH 16      9:00 a.m.—Santa Ana #2

### THE PHYSICIAN'S ASSISTANT IN CALIFORNIA

*California Medical Association Committee on  
Allied Health Personnel*

Moderator: Howard B. Kirtland, M.D., San Diego

9:00—Opening remarks

9:10—Board of Medical Examiners of California: Implementation of AB 2109—James C. MacLaggan, M.D., San Diego

9:30—Physician's Assistant: Orthopedic—John J. Niebauer, M.D., San Francisco

9:50—Paramedical Personnel: Training and Utilization—John Marshall, M.D., Torrance, by invitation

10:10—MEDEX Program in the State of Washington—Richard A. Smith, M.D., Seattle, by invitation

10:30—Equivalency Testing: Physician's Assistant in California—Michael T. B. Dennis, M.D., Stanford, by invitation

10:50—Questions and Answers Session

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TUESDAY, MARCH 16

9:00 a.m.—Santa Ana #1

### SYMPOSIUM ON EPILEPSY

*Sponsored by the Epilepsy Foundation of America, the  
Easter Seal Society, the March of Dimes*

Chairman: Robert B. Aird, M.D., San Francisco

Obstetrical Aspects of Epilepsy: Perinatal Problems

9:00—James H. McClure, M.D., Orange, by invitation

9:25—Bruce G. Berg, M.D., San Francisco, by invitation

Cerebral Maturation and Epilepsy: Changing Patterns of  
Epilepsy in Childhood: Febrile Convulsions: New Aspects  
of Petit Mal

9:45—David B. Clark, M.D., Lexington, by invitation

10:15—Bruce G. Berg, M.D., San Francisco, by invitation

The Integrated Approach to the Study and Care of Epilepsy

10:45—Richard Masland, M.D., New York City, by invitation

11:10—Douglas L. Crowther, M.D., San Francisco

11:30—Questions and Answers Session

Chairman: Edwin Boldrey, M.D., San Francisco

Problems of Diagnosis of Children, Adults, and the Aged

2:00—David Daly, M.D., Dallas, by invitation

2:40—Richard D. Walter, M.D., Los Angeles

Problems of Therapy, Including Drug Abuse

3:00—Richard Masland, M.D., New York City, by invitation

3:30—David E. Smith, M.D., San Francisco

4:00—Post-traumatic Epilepsy, Including its Legal Aspects—  
A. Earl Walker, M.D., Baltimore, by invitation

4:30—Questions and Answers Session

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TUESDAY, MARCH 16

9:00 a.m.—Costa Mesa #11

### ADOLESCENT SENSUALITY

Are Physicians and Clergymen Equipped to be Counselors?

*California Medical Association Committee on  
Medicine and Religion*

Chairman: Albert E. Long, M.D., San Francisco

PANEL DISCUSSION

Members of the Panel: To be announced



TUESDAY, MARCH 16

9:30 a.m.—Fullerton #7 and #8

## THE PHYSICIAN AND THE LEGISLATIVE PROCESS

### Symposium

*California Medical Association Commission on Legislation*

Chairman: Malcolm C. Todd, M.D., Long Beach

High-ranking legislators and Cabinet level Health Agency heads will discuss the governmental process with physicians at this Symposium.

Emphasis will be placed on the impact of government on medicine—"will we survive?", "how can individual physicians best participate in government decision-making and the legislative process?"

Minimal time will be devoted to formal presentations, with the hope of direct physician-legislator dialogue.

Participants to be announced.

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TUESDAY, MARCH 16

2:00 p.m.—Santa Ana #2

## GASTROENTEROLOGY

*Sponsored by the Southern California Society of  
Gastroenterology and the California Medical Association*

### Diseases Associated with Malabsorption

Chairman: Paul H. Guth, M.D., Los Angeles, by invitation

2:00—Causes of Malabsorption—Manley Cohen, M.D., Long Beach, by invitation

2:20—Diagnosis of Malabsorptive Disorders — Arthur D. Schwabe M.D., Los Angeles, by invitation

2:40—Management of Malabsorptive States—David G. Rimer, M.D., Los Angeles

3:00—Questions and Answers Session

3:20—Recess—Coffee will be served

### Chronic Inflammatory Diseases of the Gut

Chairman: Irwin J. Pincus, M.D., Beverly Hills

3:35—Clinical Manifestations—Harold D. Frankl, M.D., Los Angeles, by invitation

3:55—Roentgen Manifestations—Denis C. Adler, M.D., Los Angeles

4:10—Medical Management—Sheldon S. Zinberg, M.D., Pico Rivera

4:30—Surgical Management—James S. Clarke, M.D., Los Angeles

4:45—PANEL DISCUSSION

18 ONE HUNDREDTH ANNUAL SESSION

Programs for

## Section Meetings

Begin on Page 20

# 100th Annual Session

## CALIFORNIA MEDICAL ASSOCIATION

## Anaheim Convention Center

## March 13 to 17, 1971

# Scientific Sessions

## GENERAL MEETINGS

### FIRST GENERAL MEETING

SATURDAY, MARCH 13 2:00 p.m.—Santa Ana #2

#### Psychiatric Focus on Medical and Social Change

Moderator: George A. Gross, M.D., Sacramento

- 2:00—The Doctor's Place in Social Change—Howard P. Rome, M.D., Rochester, Minn., by invitation
- 2:30—Who Will be the Doctor for America's Social Ills?—Milton M. Miller, M.D., Madison, Wisc., by invitation
- 3:00—Adventures in Human Ecology—L. Jolyon West, M.D., Los Angeles, by invitation

#### PANEL DISCUSSION

Members of the Reactor Panel: George A. Gross, M.D., Sacramento; Milton M. Miller, M.D., Madison, by invitation; William A. Newsom, Jr., Davis, by invitation; Howard P. Rome, M.D., Rochester, by invitation; L. Jolyon West, M.D., Los Angeles, by invitation

### SECOND GENERAL MEETING

SUNDAY, MARCH 14 2:00 p.m.—Santa Ana #2

#### Environmental Activism—A Positive Approach

Moderator: R. Hewlett Lee, M.D., Palo Alto

- 2:00—Introduction: New Directions in Conservation—R. Hewlett Lee, M.D., Palo Alto
- 2:15—Environmental Solutions: A Congressman's Response—The Honorable Paul N. McCloskey, Washington, D.C., by invitation
- 2:45—Protecting the Environment: Role of the Federal Government for the '70's—Mr. Lewis H. Butler, Assistant Secretary for Planning and Evaluation, Department of Health, Education and Welfare, Washington, D.C., by invitation
- 3:15—Recess
- 3:30—The Physician as Environmental Activist—Rodney R. Beard, M.D., Stanford
- 4:00—Summation and Recommendations for a More Positive Approach by More Positive Physicians—Joseph F. Boyle, M.D., Los Angeles

## Acknowledgment

*THIS IS THE 100th* Scientific Assembly of the California Medical Association, and we are impressed with the enthusiasm of those planning the Scientific Section programs and other Special Conferences. There are *more* scientific and educational meetings than ever before and we believe, through the combined effort of many people, they will be *better* than ever before.

We gratefully acknowledge the cooperation of all those who have helped put this program together and feel encouraged to look forward to the second one hundred meetings.

JOHN B. DILLON, M.D., *Chairman*  
Committee on Scientific Assemblies  
of the Scientific Board

### THIRD GENERAL MEETING

MONDAY, MARCH 15 1:30 p.m.—Santa Ana #2

#### Your Continuing Education—Voluntary or Involuntary?

Chairman: Ronald L. Kaye, M.D., Palo Alto

- 1:30—Continuing Medical Education for Whom, Doctor or Patient?—George E. Miller, M.D., Chicago, by invitation
- 2:00—Community Hospital: The New Focus (or Locus) for Continuing Medical Education—Clement R. Brown, M.D., Philadelphia, by invitation
- 2:30—Physician Certification and Re-licensure—Assemblyman Gordon W. Duffy, Sacramento, by invitation
- 3:00—The CMA's Plan for Certification of Continuing Medical Education—Ronald L. Kaye, M.D., Palo Alto
- 3:30—Recess
- 3:45—Round Table Discussion—Questions and Answers  
Determination of Needs and Effects  
Of Continuing Medical Education  
Moderator: Richard W. Opfell, M.D., Santa Ana
- Members of the Panel: Clement R. Brown, M.D., Philadelphia, by invitation; Gordon W. Duffy, Sacramento, by invitation; Ronald L. Kaye, M.D., Palo Alto; George E. Miller, M.D., Chicago, by invitation; Woodbury Perkins, M.D., San Diego



# Section Meetings

## ALLERGY

*Chairman*.....E. JAMES YOUNG, M.D., San Mateo  
*Secretary*.....MILTON MILLMAN, M.D., San Diego  
*Assistant Secretary*.....HAROLD S. NOVEY, M.D., Whittier

**SUNDAY, MARCH 14**                      9:00 a.m.—Garden Grove #4

- 9:00—Psychiatric Approach to the Allergic Patient—Susan Klee-  
 man, M.D., La Jolla; Philip Solomon, M.D., La Jolla
- 9:30—Psychologic Manifestations of Allergic Disease as seen by  
 a Psychologist—Kenneth Wright, Ph.D., San Diego, by  
 invitation
- 9:50—Neurological Manifestations of Allergic Disease—M.  
 Brent Campbell, M.D., San Diego
- 10:20—Pathology of the Asthmatic States—Averill Liebow, M.D.,  
 San Diego, by invitation
- 11:20—Recess
- 11:30—New Studies Defining the Pathogenesis of Pollen Asthma  
 —Archie F. Wilson, M.D., Ph.D., Orange, by invitation

12:00—Luncheon and Business Meeting with the California So-  
 ciety of Allergy

2:15—Genetic Control of Molecular Synthesis of Polypeptide  
 Chains of Antibody—H. Hugh Fudenberg, M.D., San  
 Francisco, by invitation

3:15—Current Concepts of Delayed Hypersensitivity—William  
 B. Pincus, M.D., San Diego

4:00—Insect Allergy—Walter MacClaren, M.D., Pasadena

4:30—Provocative Food Testing—Bernard Cunningham, M.D.,  
 San Diego.

5:00—Pathology and Treatment of Status Asthmaticus

As Viewed by the Adult Allergist—Harold S. Novey,  
 M.D., Whittier

As Viewed by the Pediatric Allergist—Sheldon C. Siegel,  
 M.D., Los Angeles

## ANESTHESIOLOGY

*Chairman*.....EDWARD B. SCOTT, M.D., Los Angeles  
*Secretary*.....PAUL E. THOMAS, M.D., San Diego  
*Assistant Secretary*.....EDWIN S. MUNSON, M.D., Davis

**SUNDAY, MARCH 14**                      9:30 a.m.—Huntington Beach #6

- 9:30—Forane: Your Next Anesthetic?—Wendell C. Stevens,  
 M.D., San Francisco
- 10:15—Clinical Experience with Ketamine at Los Angeles  
 County-USC Medical Center—Harold McCloskey, M.D.,  
 Los Angeles, by invitation
- 11:00—Recess—Coffee will be served
- 11:15—Use of Large Intravenous Doses of Narcotics as Anes-  
 thetic Agents—James Schauble, M.D., San Diego, by  
 invitation

1:30—                      Panel on Malpractice

Moderator: The Honorable Leland C. Nielsen, Judge  
 of the Superior Court, San Diego, by invitation

Members of the Panel: Harold L. Engel, M.D., Esquire, Studio  
 City; David M. Harney, Esquire, Los Angeles, by invita-  
 tion; John W. McInnis, Esquire, San Diego, by invitation;  
 H. Norman Watkins, San Diego, by invitation

3:30—Business Meeting

## DERMATOLOGY

*Chairman*.....HAROLD M. SCHNEIDMAN, M.D., San Francisco  
*Secretary*.....ROBERT I. FREEDMAN, M.D., Downey  
*Assistant Secretary*.....WILLIAM M. GOULD, M.D., Palo Alto

**SATURDAY, MARCH 13**                      1:30 p.m.—Los Angeles County-  
 USC Medical Center:  
 First Floor, Women's Unit

### Pre-Convention Meeting

*There will be a combined meeting of the Los Angeles  
 and Metropolitan Dermatologic Societies. Demon-  
 stration of the patients will begin promptly at 1:30  
 p.m., to be followed by a clinical discussion of the  
 cases.*

SUNDAY, MARCH 14

8:30 a.m.—Westminster #16  
Anaheim Convention Center

Program will emphasize:

The effect of various factors in the external and internal environment, as well as the social environment, on the skin.

Chairman: Harold M. Schneidman, M.D., San Francisco

8:30—Exogenous Particles and Their Relation to Skin—Paul Hirsch, M.D., Los Angeles

9:00—Aeneiform Eruptions due to Commercial Products—Ronald Reisner, M.D., Torrance

9:30—Eruptions due to Gold Therapy—Thomas H. Rea, M.D., Los Angeles, by invitation

10:00—The Chemical Environment and the Skin—Howard I. Maibach, M.D., San Francisco

10:30—Recess

10:45—Environment and the Woman—Marjorie Bauer, M.D., Los Angeles

11:30—The Impact of the Adolescent Life Style on Cutaneous Diseases—Arnold Gurevitch, M.D., Los Angeles

Comment and Discussion: Edward Stainbrook, M.D., Los Angeles

12:30—Business Meeting

## GENERAL PRACTICE

Chairman . . . . . CLARENCE W. BURRILL, JR., M.D., Westminster  
Secretary . . . . . LESTER C. KROTCHER, M.D., San Francisco  
Assistant Secretary . . . . . A. Y. WYATT, M.D., Anaheim

SATURDAY, MARCH 13

9:00 a.m.—Santa Ana #2

*Combined Meeting with Section on Orthopedics*

9:00—Introduction: Lester C. Krotcher, M.D., San Francisco  
Chadwick F. Smith, M.D., Los Angeles

9:15—Examination of the Patient with "Backache"—William S. Stryker, M.D., San Diego, by invitation

9:45—Manipulation in Pre- and Postoperative Patients—James Henry Cyriax, M.D., London, by invitation

10:15—Recess

10:30—Therapy, Exercise, and Backache—Chadwick F. Smith, M.D., Los Angeles

11:15—PANEL DISCUSSION

Members of the Panel: Harlan C. Amstutz, M.D., Los Angeles, by invitation; Reid Bridges, Esquire, Los Angeles, by invitation; Thomas V. Girardi, Esquire, Los Angeles, by invitation; Lester C. Krotcher, M.D., San Francisco; Chadwick F. Smith, M.D., Los Angeles; William S. Stryker, M.D., San Diego, by invitation

12:00—Business Meeting—General Practice

SUNDAY, MARCH 14

9:00 a.m.—Santa Ana #2

9:00—The Internist Looks at "Backache"—Nathan E. Headley, M.D., Los Angeles

9:30—The Neurosurgical Aspects of "Backache"—Peter Dyck, M.D., Los Angeles

10:15—Recess—Coffee will be served

10:30—Choice of Patient and of Method—James Henry Cyriax, M.D., London, by invitation

Questions and Answers Session

11:00—PANEL DISCUSSION

Directed by Theodore R. Waugh, M.D., Orange

Members of the Panel: From University of California at Irvine

## GENERAL SURGERY

Chairman . . . . . JAMES W. MARTIN, M.D., Sacramento  
Secretary . . . . . MARSHALL J. ORLOFF, M.D., San Diego  
Assistant Secretary . . . . . JOHN E. CONNOLLY, M.D., Orange

MONDAY, MARCH 15

12:00 noon—Fullerton #7 and #8

12:00—Luncheon Meeting jointly with the Southern California and Northern California Chapters of the American College of Surgeons

Presiding: James W. Martin, M.D., Sacramento

12:45—Luncheon Address: Surgical Problems in the Emergency Room—James D. Hardy, M.D., Jackson, Miss., by invitation

## Emergency Room

1:15—PANEL DISCUSSION

Moderator: John E. Connolly, M.D., Orange

Members of the Panel: Albert D. Hall, M.D., Kentfield; James D. Hardy, M.D., Jackson, Miss., by invitation; Donald G. Mulder, M.D., Los Angeles

2:00—Complications Associated with Surgery

SYMPOSIUM

2:00—Shoek—Louis L. Smith, M.D., Redlands

2:15—Cardiovascular Complications—Frank H. Leeds, M.D., San Francisco

2:30—Pulmonary Problems—Edward A. Stemmer, M.D., Long Beach, by invitation

2:45—PANEL DISCUSSION

Moderator: James D. Hardy, M.D., Jackson, Miss., by invitation

3:15—Prevention and Management of Postoperative Infections—Nicholas A. Halasz, M.D., San Diego



3:45—Management of Gastroenteric Fistulae—Wiley F. Barker, M.D., Los Angeles

4:15—Diagnosis and Management of Postoperative Oliguria—Leonard Rosoff, M.D., Los Angeles

4:45—PANEL DISCUSSION

Moderator: Jack M. Farris, M.D., Los Angeles

5:00—Business Meeting

### FILM SYMPOSIUM—SURGICAL

SUNDAY, MARCH 14 2:00 p.m.—Orange County #22

### INDUSTRIAL MEDICINE AND SURGERY

Chairman.....WALTER J. GILLOGLEY, M.D., Sunnyvale  
Secretary.....REYNOLD T. SCHMIDT, M.D., Los Angeles  
Assistant Secretary...CHARLES MERCKEL, M.D., Mountain View

TUESDAY, MARCH 16 9:30 a.m.—Huntington Beach #6

#### Emotional Health in Industrial Illness

9:30—The Role of a Psychiatrist in Industry: Viewpoint of an Occupational Physician—Rufus J. Walker, M.D., Pasadena

10:00—Factors Influencing Recovery from the One-day Hernia Operation—Joseph Gaster, M.D., Los Angeles

10:30—Work as an Influence in Changing the Lives of the Hardcore Unemployed—Rodger K. Farr, M.D., Encino

11:00—Emotional Health and Industrial Illness

#### PANEL DISCUSSION

Moderator: Charles I. Barron, M.D., Burbank

Members of the Panel: Carrie E. Chapman, M.D., Los Angeles; John Gussen, M.D., Los Angeles; Irwin J. Pincus, M.D., Beverly Hills

12:00—Business Meeting

### INTERNAL MEDICINE

Chairman.....GLENN MOLYNEAUX, M.D., San Francisco

Secretary.....WILLIAM M. TODD, M.D., Long Beach

Assistant Secretary.....DANIEL W. BLACK, M.D., Hayward

SATURDAY, MARCH 13

9:00 a.m.—Orange #9

Orange #10 and Costa Mesa #11

*Presented Jointly by the Section on Internal Medicine and the Departments of Medicine, University of California, Los Angeles, Medical Center; University of California, Irvine, California College of Medicine; University of Southern California School of Medicine; and Loma Linda University School of Medicine.*

These are simultaneous and informal round table discussions, in which audience participation is anticipated. The groups will recess at 9:50 a.m. and 10:50 a.m., at which times the discussion leaders will move to a different room and continue with the same topic.

The same format will be followed on Sunday and Monday mornings

Topics and discussion leaders to be announced

### FILM SYMPOSIUM—MEDICINE

SATURDAY, MARCH 13 1:30 p.m.—Orange County #22

### OBSTETRICS AND GYNECOLOGY

Chairman.....JAMES C. CAILLOUETTE, M.D., Pasadena

Secretary.....JESSE A. RUST, JR., M.D., San Diego

Assistant Secretary....ALAN J. MARGOLIS, M.D., San Francisco

MONDAY, MARCH 15

8:30 a.m.—Garden Grove #4

### CLINICAL REPORTS

8:30—Laparoscopy as a Therapeutic Procedure—Vincent W. Cangello, M.D., Oakland

8:50—Hystero-graphy in the Detection of Hydatidiform Mole—Edward Greenbaum, M.D., Los Angeles

9:10—Diagnostic Office Suction Curettage—John L. Poyas, M.D., Newport Beach

9:30—Superficial Cone Biopsy of the Cervix—Bernard McDonald, M.D., Los Angeles

9:50—Carcinoma-Sarcoma of the Uterus—Bennett Marcus, M.D., Whittier, by invitation

10:15—Recess

*The Committee on Scientific Assemblies wishes to express thanks to the Section Program Planners for their contribution to the Annual Session. This year the various Specialty Societies and the Advisory Panels to the Scientific Sections of California Medical Association have given support and guidance in the formulation of these programs. The Committee appreciates these concerted efforts.*

- 10:30—Maternal Mortality in California: Current Status—Bruce B. Rolf, M.D., Los Angeles
- 11:00—Current Research in Fertility Control—Edward T. Tyler, M.D., Los Angeles
- 11:30—1970 California Therapeutic Abortion Report—Walter Ballard, M.D., Berkeley, by invitation
- 12:00—Joint Luncheon with the California Division of the American College of Obstetricians and Gynecologists  
Luncheon Address: Women Towards a New Identity—Sadjia Goldsmith, M.D., San Francisco, by invitation

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1:30—Joint Meeting with the Section on Psychiatry and Neurology

### Sex Research Today

#### PANEL DISCUSSION

Moderator: Sidney H. Pomer, M.D., Los Angeles

Members of the Panel: Richard Green, M.D., Los Angeles, by invitation; George A. Macer, M.D., Altadena; Sherwyn M. Woods, M.D., Los Angeles, by invitation

3:00—Recess

3:15—Business Meeting

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## OPHTHALMOLOGY

Chairman.....THEODORE STEINBERG, M.D., Fresno  
Secretary.....GEORGE K. KAMBARA, M.D., Los Angeles  
Assistant Secretary.....RUSH M. BLODGET, JR., M.D., Redding

SUNDAY, MARCH 14 1:30 p.m.—Westminster #16 and #17

### Diabetic Retinopathy

#### SYMPOSIUM

Chairman: Theodore Steinberg, M.D., Fresno

Moderator: George K. Kambara, M.D., Los Angeles

1:30—General Introduction: Problems of Diabetic Retinopathy—Bradley R. Straatsma, M.D., Los Angeles

2:00—Natural History of Diabetic Retinopathy—Matthew Davis, M.D., Madison, Wis., by invitation

2:40—Hypophysectomies for Diabetic Retinopathy—Robert W. Rand, M.D., Los Angeles

3:10—Recess

3:20—Photocoagulation in Diabetic Retinopathy—Paul C. Wetzig, M.D., Colorado Springs, by invitation

3:50—Argon and Ruby Laser Treatment of Diabetic Retinopathy—H. Christian Zweng, M.D., Palo Alto

4:20—Questions and Answers Period

4:30—Business Meeting

## ORTHOPEDICS

Chairman.....CHADWICK F. SMITH, M.D., Los Angeles  
Secretary.....HAROLD H. ROBINSON, M.D., Sacramento  
Assistant Secretary.....ROBERT D. SHLENS, M.D., Los Angeles

SATURDAY, MARCH 13

9:00 a.m.—Santa Ana #2

### Combined Meeting with Section on General Practice

9:00—Introduction: Lester C. Krotcher, M.D., San Francisco  
Chadwick F. Smith, M.D., Los Angeles

9:15—Examination of the Patient with "Backache"—William S. Stryker, M.D., San Diego, by invitation

9:45—Manipulation in Pre- and Postoperative Patients—James Henry Cyriax, M.D., London, by invitation

10:15—Recess

10:30—Therapy, Exercise, and Backache—Chadwick F. Smith, M.D., Los Angeles

11:15—PANEL DISCUSSION

Members of the Panel: Harlan C. Amstutz, M.D., Los Angeles, by invitation; Reid Bridges, Esquire, Los Angeles, by invitation; Thomas V. Girardi, Esquire, Los Angeles, by invitation; Lester C. Krotcher, M.D., San Francisco; Chadwick F. Smith, M.D., Los Angeles; William S. Stryker, M.D., San Diego, by invitation

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SUNDAY, MARCH 14

9:00 a.m.—Santa Ana #2

9:00—The Internist Looks at "Backache"—Nathan E. Headley, M.D., Los Angeles

9:30—The Neurosurgical Aspects of "Backache"—Peter Dyck, M.D., Los Angeles

10:15—Recess—Coffee will be served

10:30—Choice of Patient and of Method—James Henry Cyriax, M.D., London, by invitation

### Questions and Answers Session

11:00—PANEL DISCUSSION

Directed by Theodore R. Waugh, M.D., Orange

Members of the Panel: From the University of California at Irvine

12:00—Business Meeting

*All information as to time, place, and participants in these programs appear as supplied to us at press time. Additional information will appear in the hand program distributed to registrants at the time of the Annual Scientific Assembly.*



## OTOLARYNGOLOGY

*Chairman*. . . . . EDWARD A. KANTOR, M.D., Beverly Hills  
*Secretary*. . . . . HERBERT DEDO, M.D., San Francisco  
*Assistant Secretary*. . . . . PAUL H. WARD, M.D., Los Angeles

**SUNDAY, MARCH 14** 9:30 a.m.—Costa Mesa #12

9:30—The Surgical Treatment of Chronic Sinusitis—Berkley S. Eichel, M.D., Torrance

10:00—Laryngeal Suspension Following Supraglottic Laryngectomy—Thomas C. Calcaterra, M.D., Los Angeles

10:30—Recess

10:45—The Cavernous Angiomas of the Tympanic Membrane—Sheldon I. Freedman, M.D.; Victor Goodhill, M.D., both Los Angeles

11:15—Facial Paralysis in Children—Kedar K. Adour, M.D., Oakland

11:45—The Surgical Treatment of Obstructive Cervical Osteophytes—Muhammed H. Saffouri, M.D., Los Angeles, by invitation; Paul H. Ward, M.D., Los Angeles

12:15—Stereo Radiography of Surgical Anatomy of the Temporal Bone: Film

Authors and Discussants: Erwin Rock, M.D.; Abe Schulman, M.D.; Bernard Seife, M.D., all from Bronx, New York, by invitation

2:00—Business Meeting

### FILM SYMPOSIUM—SURGICAL

**SUNDAY, MARCH 14** 3:20 p.m.—Orange County #22

Pre-Adenotonsillectomy Cinefluorography—Richard T. Barton, M.D., Beverly Hills, and Stanley W. Brummett, M.D., Santa Monica

## PATHOLOGY

*Chairman*. . . . . HARRY J. SACKS, M.D., Los Angeles  
*Secretary*. . . . . OSMAN H. HULL, M.D., Monterey  
*Assistant Secretary*. . . . . ROBERT S. COX, JR., M.D., San Jose

**THURSDAY, MARCH 11** 12:00 noon—Room to be announced

12:00—Luncheon and Meeting with the AMA-Approved Schools of Medical Technology

**SATURDAY, MARCH 13** 9:00 a.m.—Fullerton #7 and #8

### Review of Recent Status of Hormone Testing in Clinical Medicine

Moderator: Gerson R. Biskind, M.D., San Francisco

9:00—Principles of Competitive Protein Binding Assays for Analysis of Hormones—William D. Odell, M.D., Ph.D., Torrance, by invitation

9:20—Interpretation of Aldosterone Levels—Edward G. Biglieri, M.D., San Francisco

9:40—Evaluation of Renin Angiotensin System in Clinical Disorders—Edward G. Biglieri, M.D., San Francisco

10:00—Measurement of Androgens—Richard Horton, M.D., Los Angeles, by invitation

10:20—LH, FSH and Chorionic Gonadotropin—William D. Odell, M.D., Ph.D., Torrance, by invitation

10:40—Questions and Answers Session

10:50—Recess

11:10—Growth Hormone—Selma L. Kaplan, M.D., San Francisco, by invitation

11:30—Role of Serum Insulin in the Diagnosis and Management of Hyperglycemic States—John Karam, M.D., San Francisco, by invitation

11:50—Parathormone—John E. Bethune, M.D., Los Angeles, by invitation

12:10—Plasma ACTH Determinations by Radioimmunoassay—C. D. West, M.D., Salt Lake City, by invitation

12:30—Thyroxine, LATS and Thyroid Autoantibodies—David H. Solomon, M.D., Torrance, by invitation

12:50—Questions and Answers Session

2:00—Business Meeting—Section on Pathology

2:15—Business Meeting—California Society of Pathologists

**SUNDAY, MARCH 14**

9:00 a.m.—Garden Grove #3

## PATHOLOGY CONFERENCE

*Sponsored by the American Cancer Society, California Division;  
the California Medical Association Committee on Cancer;  
Member Pathologists, Los Angeles County-USC Medical Center*

### Central Nervous System and Spinal Cord Tumors

Moderator: Richard M. Davis, M.D., Los Angeles

Participants: Clark Fobes, M.D., San Bernardino, by invitation;  
Roger Terry, M.D., Los Angeles, by invitation

9:30 a.m. to 12:30 p.m.

2:00 p.m. to 5:30 p.m.

The registration fee for this Conference is \$30.00, which includes attendance, a set of 25 slides, protocol and addenda. For attendance only, the fee is \$15.00. There is no charge for residents and interns. Those wishing to attend are requested to register with Weldon K. Bullock, M.D., Executive Director, Tumor Tissue Registry, Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033.

## PEDIATRICS

*Chairman* . . . . . CHESTER TANCREDI, M.D., San Diego  
*Secretary* . . . . . WILLIAM M. JENKINS, M.D., Oakland  
*Assistant Secretary* . . . . . J. HAROLD BATZLE, M.D., Riverside

MONDAY, MARCH 15 9:00 a.m.—Garden Grove #3

### Pediatrics and Child Psychiatry

Moderator: Thomas L. Trunnell, M.D., San Diego

9:00—Introduction

9:10—Video Tape Presentation—"Live" patient material, specially produced in collaboration with Pediatricians and Child Psychiatrists

9:45—Recess

10:00—Video Tape Presentation—continued

11:00—Recess

11:15—Panel Discussion and Questions and Answers Session

Discussants:

Early Developmental Problems—Alan E. Shumaker, M.D., San Diego; Thomas L. Trunnell, M.D., San Diego  
Problems of Learning Disabilities—Frederick A. Frye, M.D., San Diego; LeRoy F. Kurlander, M.D., San Diego  
Problems of Drug Abuse—William W. Baak, M.D., San Diego, by invitation; David L. Chadwick, M.D., San Diego

MONDAY, MARCH 15 12:00 noon—Garden Grove #3

12:00—Luncheon with the American Academy of Pediatrics, District IX

Moderator: Saul J. Robinson, M.D., San Francisco

Luncheon Address: The Pediatrician and the New Physician's Assistant Law—James C. MacLaggan, M.D., San Diego

MONDAY, MARCH 15 1:30 p.m.—Garden Grove #3

### Drugs and Youth

1:30—Introduction—J. Thomas Ungerleider, M.D., Los Angeles

1:45—How the Pediatrician Approaches the Problems of Drug Abuse—Clifford L. Rubin, M.D., Beverly Hills

2:00—Counseling Youth—Arnold H. Zukow, M.D., Encino

2:15—Sample Dialogue—Doctors Rubin, Ungerleider and Zukow and two youth representatives, one an ex-user and the other a non-user

4:30—Business Meeting

## PHYSICAL MEDICINE AND REHABILITATION

*Chairman* . . . . . ROBERT V. MILLER, JR., M.D., Encino  
*Secretary* . . . . . JOSEPH N. VIZZARD, M.D., Los Gatos  
*Assistant Secretary* . . . . . CARRIE E. CHAPMAN, M.D., Los Angeles

SUNDAY, MARCH 14 9:00 a.m.—Westminster #17

### Less Known Diagnostic and Prognostic Procedures Useful in the Practice of Medicine

9:00—Introductory Remarks—Robert V. Miller, Jr., M.D., Encino

9:10—Action Potential Analysis in Clinical Electromyography—Michael Fearnley, M.D., Hamilton, Ontario, by invitation

9:40—Thermography and Plethysmography: Diagnostic Importance and Techniques—Travis Winsor, M.D., Los Angeles

10:40—Recess

10:55—Sensory Conduction Velocities in Differential Diagnosis of Nerve Lesions—Michael Carpendale, M.D., West Haverstraw, New York, by invitation

11:30— PANEL DISCUSSION

Moderator: Robert V. Miller, M.D., Encino

12:00—Business Meeting

## PLASTIC SURGERY

*Chairman* . . . . . DONALD HAUSE, M.D., Sacramento  
*Secretary* . . . . . DONALD E. BARKER, M.D., Van Nuys  
*Assistant Secretary* . . . . . RAYMOND R. KAUFFMAN, M.D., San Mateo

SUNDAY, MARCH 14 9:00 a.m.—Fullerton #7 and #8

### The Role of Plastic Surgery in Medicine

9:00—Soft Tissue Defects in Vietnam War Casualties—Stanley C. Morgan, M.D., Pasadena, by invitation

9:20—Management of Tumors of the Nasal Tip—Harry J. Buncke, Jr., M.D., San Mateo

9:40—Studies in Wound Healing—Franklin L. Ashley, M.D., Los Angeles

10:00—Evaluation of Hypospadias Repair—Robert E. Berner, M.D., Palo Alto

10:20—Carcinoma of the Breast Mistaken for Mastitis—Donald J. Mangus, M.D., Chico

10:40—Recess

11:00—Secondary Rhinoplasty—Jack H. Sheen, M.D., Beverly Hills

11:20—Selected Use of Post-Auricular Tube Pedicle in Ear Reconstruction—Orrin S. Cook, M.D., Sacramento



- 11:40—Treatment of Ectropion of the Paralyzed Lower Eyelid—  
Salvador Castanares, M.D., Los Angeles
- 12:00—Management of Maxillo-Facial Injuries—Raymond R.  
Kauffman, M.D., San Mateo
- 12:20—Luncheon
- 1:30—Management of Facial Skin Tumors—William R. Shadish,  
M.D., Redding
- 1:50—Management of Head and Neck Malignancy—Hugh H.  
Crawford, M.D., Santa Ana
- 2:10—Other topics and speakers to be announced
- 4:30—Business Meeting

## PREVENTIVE MEDICINE AND PUBLIC HEALTH

Chairman.....GLEN W. KENT, M.D., Martínez  
Secretary.....STEPHEN A. CORAY, M.D. Ventura  
Assistant Secretary.....RICHARD SVIHUS, M.D., Santa Cruz

**TUESDAY, MARCH 16** 9:00 a.m.—Garden Grove #3

### Teen's Troubles—Is There a Way Out?

Chairman: Stephen A. Coray, M.D., Ventura

- 9:00—Introduction: The Problems—Roland Summitt, M.D.,  
Torrance, by invitation
- 9:20—The Pregnant Teen-Ager: Social Aspects—Mrs. Gorgiana  
Selstad, Ventura, by invitation
- 9:40—The Pregnant Teen-Ager: Medical Aspects—Dimitry V.  
Prian, M.D., Torrance, by invitation
- 10:00—Recess
- 10:15—Drugs, Teen-Agers, Treatment—Edward R. Bloomquist,  
M.D., Glendale
- 10:45—College Crisis—David P. Gardner, Ph.D., Santa Barbara,  
by invitation
- 11:45—Prevention—Roland Summitt, M.D., Torrance, by invita-  
tion
- 1:00—Business Meeting

*DAILY SCHEDULE of events appears on pages 2 and 3.*

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*Listing and description of Scientific and Organizational  
Exhibits appear on pages 30 to 33.*

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*Out-of-State Guest Speakers and all other participants  
known at this time are listed on pages 7 to 11.*

★

*Special Conferences are listed on pages 12 to 18.*

## PSYCHIATRY AND NEUROLOGY

Chairman.....SIDNEY H. POMER, M.D., Los Angeles  
Secretary.....MORTON K. RUBINSTEIN, M.D., Los Angeles  
Assistant Secretary.....NORMAN I. GRAFF, M.D., San Mateo

**MONDAY, MARCH 15** 9:00 a.m.—Westminster #16 and #17

### Commonly Missed Psycho-Physiologic Problems

#### SYMPOSIUM

- 9:00—Moderator: Sidney H. Pomer, M.D., Los Angeles
- Participants: Lailee B. Bachrach, M.D., Los Angeles; William F.  
Keily, M.D., Los Angeles; Charles W. Wahl, M.D., Los  
Angeles, by invitation

### Man's Most Common Ailment: HEADACHE

#### SYMPOSIUM

- 10:40—Moderator: J. Carroll Ramseyer, M.D., Los Angeles
- Participants: Daniels D. Hansen, M.D., Marina del Rey; Edward  
H. Liston, M.D., Los Angeles, by invitation; Louis J.  
Rosner, M.D., Beverly Hills
- 12:00—Lunch

**MONDAY, MARCH 15** 1:30 p.m.—Garden Grove #14

1:30—Joint Meeting with the Section on Obstetrics and Gynecology

### Sex Research Today

Moderator: Sidney H. Pomer, M.D., Los Angeles

Members of the Panel: Richard Green, M.D., Los Angeles, by  
invitation; George A. Macer, M.D., Altadena; Sherwyn  
M. Woods, M.D., Los Angeles, by invitation

#### PANEL DISCUSSION

3:00—Recess

3:10—Reconvene in Westminster #16 and #17

### Recent Trends in Cerebrovascular Disease

#### SYMPOSIUM

- 3:10—Moderator: J. Carroll Ramseyer, M.D., Los Angeles
- Participants: David B. Clark, M.D., Lexington, by invitation;  
Morton Cooper, Ph.D., Los Angeles, by invitation; Philip  
T. White, M.D., Milwaukee, by invitation
- 4:40—Business Meeting

## RADIOLOGY

*Chairman*.....MATHEW E. O'KEEFE, JR., M.D., Whittier  
*Secretary*.....WARREN M. RUSSELL, M.D., San Francisco  
*Assistant Secretary*.....GABRIEL H. WILSON, M.D., Los Angeles

**SATURDAY, MARCH 13 9:30 a.m.—Orange County #21**

### Radiology Conference

*Committee on Cancer, California Medical Association*

9:30 a.m. to 12:00 noon—**THERAPY SESSION**

Moderator: R. Wilbur Melbye, M.D., Los Angeles

1:30 p.m. to 3:30 p.m.—**DIAGNOSTIC SESSION**

Coordinator: D. E. Blickenstaff, M.D., La Jolla

**SUNDAY, MARCH 14 9:00 a.m.—Orange County #21**

9:00—**The Importance of the Fat Pad Sign in a Variety of Diseases of the Elbow**—Roger J. Jackman, M.D., Palo Alto

9:20—**Angiography of the Adrenals**—Stewart R. Reuter, M.D., San Diego, by invitation

9:40—**A Medical Community Looks at Carcinoma of the Cervix**—James W. Rowe, M.D., Santa Barbara

10:00—**Pelvic Pneumography in Children**—Michael T. Gyepes, M.D., Los Angeles

10:20—**Recess**

10:40—**Pharmaco-Radiology of the Gastrointestinal Tract**—Douglas Sheft, M.D., San Francisco

11:00—**The Uses of Radioisotopes in Liver Disease**—Jan K. Siemsen, M.D., San Pedro, by invitation

11:20—**Protection of the Kidney and Small Bowel in Radiation Therapy Using an Arterial Catheter**—Richard J. Steckel, M.D., Los Angeles

11:40—**Occult Spinal Dysraphism**—Henry F. W. Pribram, M.D., Long Beach, by invitation

12:00—**Business Meeting**

**SUNDAY, MARCH 14 2:00 p.m.—Orange County #21**

### Fifth Annual L. HENRY GARLAND MEMORIAL LECTURE

*Sponsored by the California Radiological Society*

2:00—**Introduction**—Charles G. Campbell, M.D., La Jolla

2:05—**New Approaches to the Analysis of Cancer Data**—Antolin Raventos, M.D., Davis, by invitation

3:00—**Recess**

3:15—**Annual Meeting**—California Radiological Society

## UROLOGY

*Chairman*.....JAY R. LONGLEY, M.D., Newport Beach  
*Secretary*.....ROBERT A. C. BRIDGE, M.D., San Diego  
*Assistant Secretary*.....JAMES H. PULFORD, M.D., Salinas

**MONDAY, MARCH 15 9:00 a.m.—Huntington Beach #6**

9:00—**Bladder Physiology**—Emil A. Tanagho, M.D., San Francisco, by invitation

9:45—**Renal and Adrenal Angiography**—James W. Lecky, M.D., Los Angeles

10:30—**Current Concepts of Normal Renal Physiology**—Lester Klein, M.D., Los Angeles, by invitation

11:00—**Recess**

11:15—**Abnormal Renal Physiology**—James Orecklin, M.D., Los Angeles, by invitation

11:45—**Questions and Answers Session**

Moderator: Stanley A. Brosman, M.D., Torrance

12:15—**Business Meeting**

12:30—**Luncheon**

1:30—**Bladder Physiology of Urinary Tract Infection**—Emil A. Tanagho, M.D., San Francisco, by invitation

2:00—**Radiologic Aspects of Urinary Tract Infection**—Duncan Craven, M.D., Los Angeles, by invitation

2:25—**The Urethra, and its Relation to Urinary Tract Infection**—Bimal K. Masih, M.D., Torrance, by invitation

2:45—**Recess**

3:00—**The Prostate: Its Relation to Urinary Tract Infection**—Edwin M. Meares, Jr., M.D., Palo Alto, by invitation

3:30—**The Unsuspected Neurologic Disorder as a Cause of Urinary Tract Infection**—Donald C. Martin, M.D., Torrance

4:00—**Newer Antibiotics in Urology**—Irwin Ziment, M.D., Torrance

4:30—**Questions and Answers Session**

Moderator: Stanley A. Brosman, M.D., Torrance



# MOTION PICTURE PROGRAM

## Orange County # 22

### Co-Chairmen

Richard E. Gardner, M.D., San Francisco

W. Morris H. Noble, M.D., San Francisco

Three film symposia will be presented, each utilizing about two-thirds of the time for projecting of films, and one-third for discussion, questions and answers.

SATURDAY, MARCH 13

### MEDICINE

Moderator: To be announced

#### 1:30—Introduction:

1:35—**Symptomatic Postgastrectomy Stomach**—Basil I. Hirschowitz, M.D., Birmingham

Shows how the fibroscope can be used to detect, define and delineate postoperative complications in the gastrectomy patient. Dr. Hirschowitz provides original photography of his patients. 22 minutes.

Discussant: Martin Brotman, M.D., San Francisco

2:40—**Lillehi on Stagnant Shock**—Richard C. Lillehi, M.D., Minneapolis, Ronald H. Dietzman, M.D., Minneapolis, Ted Bond, Professor, University of Texas, Galveston

Through the use of vivo cinemicrography of the mesentery micro circulation of dogs, Bond and Derrick of the University of Texas illustrate the physiologic manifestation of endotoxin shock on the cellular level and the comparative effects of the administration of plasma alone, plasma-plus-vasopressor, and plasma-plus-vasodilator. The scene shifts to the University of Minnesota Hospital where Lillehi and Dietzman explain and demonstrate the step by step management of an actual patient in stagnant endotoxin shock secondary to septic abortion. 25 minutes.

Discussant to be announced.

3:00—**Reasonable Expectations in the Management of Diabetes**—T. S. Danowski, M.D., Pittsburgh

This film delineates an innovative, easily comprehended approach to diagnosis throughout the diabetic spectrum, then relates the options in treatment to the several diagnostic categories established earlier, and finally presents an assessment of reasonable expectations in management based on our present knowledge of the disease process and the therapeutic tools now available. 25 minutes.

Discussant to be announced.

Other films to be announced.

SUNDAY, MARCH 14

### SURGERY

Moderator: Richard E. Gardner, M.D.

#### 2:00—Introduction

2:05—**Dacron-Silicone Prosthesis Replacement of Metacarpophalangeal Joints**—John L. Niebauer, M.D., San Francisco

The need for an efficacious prosthetic metacarpophalangeal joint is outlined and the specifications for such a prosthesis explained. Development and testing of such a prosthesis is described. Implantation procedure is shown. Operative procedure for implanting multiple prostheses is demonstrated. 15 minutes.

Discussant to be announced.

2:40—**Cancer of the Urinary System**—Willett F. Whitmore, Jr., M.D., New York

Reviews the signs and symptoms of urothelial and renal cell cancers. Diagnostic procedures including radiologic and cytologic techniques and cystoscopy are shown. Principles of therapy, choice of modality, and end results are discussed. 20 minutes.

Discussant to be announced.

3:20—**Pre-Adenotonsillectomy Cinefluorography** — Richard T. Barton, M.D., Beverly Hills, and Stanley W. Brummett, M.D., Santa Monica.

This picture is designed to alert surgeons to the danger of post-operative velopharyngeal incompetence following T&A. This is becoming an ever-increasing medico-legal hazard. Certain pre-operative factors are emphasized and warning signals for such potential complication. 11 minutes.

Discussant: Richard T. Barton, M.D., Beverly Hills.

Other films to be announced.

## GENERAL

Moderator to be announced

### 2:00—Introduction

2:05—**Depression**—Sir Denis Hill, D.P.M., Professor, University of London, London, Leo E. Hollister, M.D., Palo Alto, et al.

A new medical film that explores this difficult subject with up-to-date information. Sir Denis Hill, Dr. Hollister, and others describe the contemporary history of depression in a first-person documentary format with immediate clinical relevance. This provides a current insight into the clinical implications of depression. A monograph and self-evaluation test will be provided on request.

Discussant to be announced.

2:45—**Drug Abuse: One Town's Answer**—Charles Cahill, Hollywood

This film shows the results when two young reformed drug users were brought into a town to set up a program for drug education. The film centers around Awareness House where young people could meet to discuss their problems and find answers to their questions. The film shows the program in action with teens openly exploring their experiences. The film lays stress on the needs for such avenues of frank conversation where young people can gain strength and find willing listeners through one another. 16 minutes.

Discussant to be announced.

4:00—**Emergency Ambulance Service, Organization and Operation**—American College of Surgeons

The purpose of this film is to show the public what good emergency ambulance services are like, who runs them, and what some of the organizational and operational problems are so that communities may be better able to evaluate their own local services and see where they should be improved. 25 minutes.

Discussant to be announced.

Other films to be announced.

You may be reached through  
(714) 635-8440

### EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(714) 635-8440.

From 9:00 a.m. to 5:00 p.m., Saturday, March 13 through Wednesday, March 17.

### MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company—(714) 635-8440.

*Location:* South Lobby, Anaheim Convention Center.

*Hours:* 9:00 a.m. to 5:00 p.m.

The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the Convention number.

*Routine Messages:* Will be kept at the Message Center in the South Lobby, Anaheim Convention Center.

Physicians are *requested* to *check with the Message Center at least once a day.*

## To Register — You MUST have proper identification

### QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION:

*All M.D.s* with credentials showing that they hold valid license to practice medicine. (Membership card: CMA; county medical society/association; AMA.)

*Medical students* upon presentation of credentials from their medical schools. (Membership card, Student Medical Association, or letter from Dean's office.)

*Medical Assistants* upon presentation of a letter from the physician-employer or C.M.A.A. membership card.

*Military paramedical personnel* upon presentation of a letter requesting their admittance, written by their commanding officer.

*Dentists (D.D.S.)—Doctors of Veterinary medicine (D.V.M.)—registered nurses (R.N.)—student nurses—x-ray technicians—laboratory technicians—allied public health personnel—and others* will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.



# Scientific and Organizational Exhibits

## Grand Lobby, Anaheim Convention Center

**An Adventure in International Medicine: A Changing Role for the Peace Corps Physician**—Edward J. Klecker, Washington, D.C., by invitation. A four-panel exhibit describes the salaried opportunities open to physicians and Registered Nurses who are hired for 2- or 3-year assignments to provide health care systems for Peace Corps Volunteers in approximately 59 countries. The second purpose of the display is to describe the public health role Peace Corps Physicians carry out in developing areas while serving on the Peace Corps staff.

**Angiography of Stroke**—Jack Eisenman, M.D., Irvine, by invitation. Display illustrates case material demonstrating the application of angiography to the diagnosis of cerebrovascular occlusive disease.

**Ankylosing Spondylitis: Diagnosis and Management**—John J. Calabro, M.D., Worcester, Mass., by invitation. The earlier the diagnosis of ankylosing spondylitis, the more favorable the outcome of management. Early recognition depends on the determination of diminished spine flexion, reduced chest expansion, and clinical and x-ray evidence of sacroiliitis. A carefully individualized program of management must include antirheumatic drugs, postural training, and remedial as well as recreational exercises.

**The Antiquity of Gout**—John H. Talbott, M.D., Chicago, by invitation. Since gout has been recognized as a clinical entity since before the birth of Christ, many paintings, cartoons and caricatures have been produced. These form the basis of our exhibit, which also presents a brief text on early misconceptions about gout and milestones in its diagnosis and management.

**Area II Regional Medical Programs (University of California at Davis)**—Neil C. Andrews, M.D., Davis. A) Large scale map of Area II with colored dots marking the locations of education and training programs in remote and outlying hospitals. B) Series of posters and charts listing those activities using colored dots to show the pattern of planning and programming by RMP in Northern California.

**California Medical Assistants Association**—Lorraine Rumpfer, San Francisco, by invitation. Brochures explaining the benefits of American Association of Medical Assistants and California Medical Assistants membership and the educational program, which includes in-service education, the Certification of qualified assistants, and professionalism of medical assistants.

**California Medical Association Medical Staff Survey Committee**—Ted Harris, San Francisco, by invitation. Charts and photographs provide a capsule history and illustrate objectives and implementation of the on-going evaluations of medical care in California hospitals and long-term care facilities. Handout materials will be available.

**California Society of Plastic and Reconstructive Surgeons**—Raymond R. Kauffman, M.D. Burlingame. Screen projection and voice-synchronized description and discussion of interesting problems faced by the plastic and reconstructive surgeon.

**Cancer: Youth Education Exhibit**—Glenn I. Hildebrand, San Francisco, by invitation. Focused on cancer prevention and control, this exhibit is developed by youth groups from the Los Angeles Unit of the American Cancer Society.

**Childbirth at Home**—Joseph Franklin Griggs, M.D., Claremont. A continuously-running silent motion picture film showing an unrehearsed documentary of an uncomplicated delivery of a secunda gravida in the home with all the necessary preparations. The training instructions to the mother and father are repeated after labor begins by the physician and the nurse midwife in attendance. The method of inspecting for lacerations and making repairs, if needed, is illustrated.

**The Clinical Use of a Frozen Semen Bank**—Edward T. Tyler, M.D., Los Angeles. This exhibit reviews approximately 12 years experience with frozen semen in clinical practice. The techniques of freezing and methods of storage are presented covering the use of frozen-thawed semen alone in artificial insemination. The use of pooled concentrated frozen-thawed oligospermic semen is also discussed.

**Color Television as a Teaching Aid in Gastroscopy**—J. Alfred Rider, M.D., San Francisco. Closed circuit color television of the stomach is an invaluable teaching and diagnostic aid. It offers the advantage of immediate availability of the intragastric scene to an unlimited number of students and provides for instantaneous consultation with other qualified observers. It thus allows for simultaneous observation and interpretation of gastric findings and the opportunity for immediate playback of the recorded scene.

**Control of Medical Quackery: California State Department of Public Health**—Lewis Saylor, M.D., Berkeley. It is planned to display fraudulent diagnostic and therapeutic devices used in medical quackery in this state. These devices are very interesting and reflect ingenious complexity and pseudo-scientific bases.

**Cryosurgery: The "Cool" Approach to Head and Neck Surgery**—Hans von Leden, M.D., Los Angeles. Cryosurgery—the utilization of controlled intense cold for the destruction of diseased tissue, has progressed to an advanced developmental phase. The exhibit presents the author's clinical and experimental data, the technique of cryosurgery, and its application to surgery of the nose, mouth, throat, and face. The clinical indications for cryosurgery are presented.

**Cystic Fibrosis**—Paul A. Di Sant'Agnese, M.D., Bethesda, Md., by invitation. This exhibit presents the results of work on cystic fibrosis by scientists of the National Institute of Arthritis and Metabolic Diseases. Included are diagrams of the glands and other organs involved in the disease and a sequence on general body involvement; X-rays showing this progression in the lungs; and a series of charts and graphs giving the data collected during the course of the study. In addition, diagnostic criteria are presented and outlines of treatment are suggested.

**Diabetic Foot Ulcer: An Aggressive Approach**—Robert S. Ozeran, M.D., Los Angeles. This exhibit depicts an aggressive approach that has been developed by the authors for the treatment of diabetic foot ulcers, infections, and gangrene which can be successfully employed in patients who do not have compromised major arteries. Patients are selected on the basis of and findings on clinical examinations, and electric monitoring of the circulation. Aggressive debridement is employed in patients with adequate circulation with almost 100 percent healing rate. In most patients with poor circulation, a major amputation is performed. Through the use of this technique, major amputations are avoided in many patients who would otherwise be subjected to them, while patients requiring amputations can be started on their rehabilitation program.

**Diagnose Gout and Treat It**—Irvin F. Hermann, M.D., Philadelphia, by invitation. This exhibit presents the comprehensive management of patients with gout with special emphasis on specific detailed therapy for the initial acute attack, subsequent acute attacks and long term management. The patient's presenting symptoms are considered and the method of making a diagnosis both presumptive and positive is outlined. Several roentgenograms, photomicrographs and pictures of gross specimens illustrate the basis for a positive diagnosis. With an increased awareness by the physician for a "complete prescription for gout" effective management of the gouty patient can be insured.

**Disability Evaluation under Social Security**—Benjamin Lieberman, M.D., Oakland. This is a new and up-dated version depicting the principles and procedures followed in making determinations for allowance or denial of benefits under this federal program. It is supplemented with slides showing the medical eligibility criteria. Pertinent pamphlets will be distributed.

**Drug Interactions**—Roland E. Lapointe, M.D., Chicago, by invitation. This exhibit will bring to the attention of the practicing physician the importance of being alert to the hazards of drug interactions. Mechanisms and examples of drug interactions will be shown. Physicians will be able to sign up for literature on this subject at the exhibit.

**Drug Treatment of Hyperlipidemia**—Donald Berkowitz, M.D., Philadelphia, by invitation. Although dietary changes may lower blood lipids, in the usual poorly motivated patient, drug therapy is much more acceptable. This exhibit describes the normal metabolism of cholesterol, and summarizes the indications, specific lipids affected, dosage, side effects, and mechanisms of action of the currently available hypolipidemic drugs. Results in the management of over 500 patients with this condition indicate that clofibrate is the drug of choice for the management of hyperlipidemia. Normalization of the serum cholesterol and triglycerides may

be achieved in over 75 percent of those treated with this preparation without any dietary restrictions. The other drugs may be reserved for those patients who fail to respond to clofibrate therapy.

**"Eat Well . . . Eat Wisely"**—Warren H. Braden, San Francisco, by invitation. American Heart Association film to alert physicians, nurses, dieticians, and hospital staff to AHA publications for the general public on food selection and meal planning designed to reduce the risk of heart attack.

**Effect of Diazepam on Meperidine Requirements During Labor**—Kenneth R. Niswander, M.D., Davis. A group of 189 patients in early labor was studied to determine whether diazepam would reduce meperidine requirements without deleterious effects on the newborn. Test medication consisted of either diazepam or placebo administered intravenously in double-blind fashion. Maternal effects evaluated included blood pressure, pulse, level of consciousness, degree of analgesia, and recall of procedure. Infants were examined for signs of respiratory depression or other abnormalities, and Apgar scores were recorded. There was a statistically significant reduction in meperidine dosage requirements, in level of consciousness, and recall of labor and delivery. Diazepam was well tolerated by both mother and infant during labor.

**Enhanced Living for the Withdrawn Schizophrenic**—Robert M. Ritter, M.D., Whitfield, Miss., by invitation. This exhibit presents some problems of management and a rational approach to drug therapy for chronic, withdrawn, anergic, depressed patients. Results of a double-blind crossover study will also be presented. Case histories on several regressed schizophrenic patients who showed reversal of symptoms for the first time as the result of a treatment program will be presented.

**Epilepsy: A Graphic Presentation of its Medical, Social and Legal Aspects**—Mrs. Betts Jensen, by invitation. Seizure patterns, age of onset, initial and secondary seizure cycle, intelligence rating, correlation between age of onset and possible cause. Comparison to other neurologic disorders. Socio-legal aspects—public attitudes—legal restrictions faced.

**Explorer Scouting: Medical**—J. V. Anglin, M.D., Merced. Scientific exhibit of current project, objectives and activities of Explorer Scout youths.

**Family Life Education in San Mateo County: A Multi-disciplined Effort**—Walter Smithley, Redwood City, by invitation. We will describe the development and implementation of Family Life Education from an approach involving physicians, psychologists, theologians, educators, and a broad array of citizen volunteers. Problems encountered and alternative approaches will also be dealt with. Slides, tapes, pictorial displays, and descriptive literature are used.

**Group Practice Prepayment: A Modern Prototype**—Robert Gunbinder, M.D., Long Beach. A pilot project for the provision of covered services under Medi-Cal/Medicaid. This exhibit will demonstrate the need, planning, organization, and operation in creating and utilizing a small existing group practice in Southern California for the provision of Title 19 services to an inner city population of Long Beach on a pre-paid capitation basis. Graphics, audio visual, and literature are employed.



**Helicopter Evacuation of Highway Injuries**—Edward R. Jenkins, M.D., Elk Grove, Calif. The exhibit is composed of an actual MediVac helicopter with its ancillary equipment, including a night sun-light suspended overhead to illuminate the exhibit. There will also be a continuous motion picture film outlining the use of the 'copter for emergency evacuation.

**Hypertension and its Complications**—Albert N. Brest, M.D., Philadelphia, by invitation. The major complications of hypertensive disease include: Cardiac failure, renal decompensation, angina pectoris, strokes, malignant hypertension, and the various hypertensive emergencies. The exhibit reviews the pathophysiology and therapy of these complications. In addition, the use of bilateral carotid sinus nerve stimulation in drug-resistant hypertension is described.

**Improved X-ray Interpretation of Joint Disease**—David L. Berens, M.D., Buffalo, by invitation. Radiographs of joints are not often used to full advantage in diagnosis of rheumatoid arthritis and ankylosing spondylitis. The physician must know the sites of involvement and be familiar with changes that occur in these diseases. This exhibit presents the sites and changes through use of radiographs and diagrams.

**Isotope Cisternography**—J. Powell Williams, Jr., M.D., Irvine, by invitation. Eight bank view boxes presenting results of studies of primary and secondary indications for isotope cisternography.

**Joint Fluid Analysis**—Andrea Cracchiolo III, M.D., Los Angeles, by invitation. Of the many parameters used to identify and measure disease states, analysis of joint fluid is either incomplete or completely overlooked. The exhibit will describe tests now available, disease states in which they are indicated, and interpretation of results. Most important will be a description of proper collection of fluid.

**Management of Cerebral Atherosclerosis**—Francis H. Stern, M.D., Philadelphia, by invitation. Atherosclerosis is frequently an etiological factor, producing symptom-combinations in geriatric patients with emotional disturbances. An 8-week double-blind cross-over study of 30 geriatric patients utilizing a combination of potassium iodide and niacinamide hydroiodide vs. placebo was performed and the drug preparation gave significant improvement in the anxiety expression, behavior disorders and associated depression complexes.

**Management of Lumbosacral Pain**—Lee J. Cordrey, M.D., Tampa, by invitation. Presented in this exhibit is the evaluation of management on 573 patients treated for back pain. The evaluations were made during a 12-month period and treatment was rendered for specific pathologic entities. Spine fusions were performed on thirteen patients and the fusions were explored four to six months post surgery. Pseudarthrosis was found in six patients. Exploration of the fusion mass and effective therapy makes early rehabilitation feasible. Comprehensive management and result of treatment are presented for the non-surgical patients.

**Medic Alert Foundation: Emergency Medical Identification**—Alfred A. Hodder, Turlock, Calif., by invitation. This exhibit is presented to stimulate professional awareness of the Medic Alert emblem. It also emphasizes the need for physicians to urge patients with special or "hidden" medical problems to wear a Medic Alert emblem. The function of the Foundation's 24-hour computerized Central Registry, which gives medical facts in an emergency about any wearer to qualified personnel, free of charge, is also explained.

**The National Foundation-March of Dimes Research and Center Program**—W. Dean Lindgren, M.D., Santa Ana. Continuous showing of the youth education film "More Than Love," previewed by a number of physicians and found acceptable for use in elementary through high school and college.

**A New Concept in Antibiotic Therapy in Pediatrics**—Jan Alban M.D., San Francisco. Where the usual routes of administering a needed antibiotic are unavailable or undesirable, per rectum has been shown to be an advantageous route by the results achieved in these studies. The new erythromycin suppositories (125 mg) provided efficacious therapy without serious or limiting side effects.

**A New Form of Thyroid Replacement Therapy**—William A. Abelow, M.D., Coral Gables, by invitation. The objectives of this exhibit are to review the several forms of thyroid replacement therapy and their effect on usual tests for thyroid function. A new form of synthetic thyroid replacement therapy is presented that combines both thyro-active hormones (sodium levothyroxine and sodium liothyronine) in a ratio which simulates normal endogenous secretion. This new synthetic (liotrix) produces P.B.I.'s and other thyroid function test values which fall within the normal range.

**"New" Gonorrhea: Stubborn or Resistant?**—Morton Nelson, M.D., Oakland. Though penicillin has lost some of its once overwhelming effectiveness against *Neisseria gonorrhea*, resistance has proved relative. Results with 225 patients at the Alameda County Health Department VD Clinic in Oakland have borne out this hypothesis. A sequel study involving 332 male patients confirms the conclusion reached in our earlier experience with the 225 patients.

**Pollution—Medical Research Association of California.** Concerning the effects of pollution. Photos and legend courtesy of Russell P. Sherwin, M.D., of University of Southern California, Los Angeles, by invitation.

**Recovery Room Analgesia Without Narcotics**—George Wallace, M.D., Brooklyn, by invitation. This exhibit presents a clinical evaluation of 824 patients given a potent analgesic in the recovery room for postoperative pain.

**Reduction of CSF Pressure by Chemotherapy: A Comparative Study**—H. Hooshman, M.D., Richmond, Va., by invitation. A comparative study of effects of mannitol and dexamethasone on cerebral spinal fluid (CSF) pressure was done in dogs with and without intra-cerebral hemorrhage. By use of animated illustrations the exhibit shows that, in the presence of a focal lesion in the brain, steroids decrease CSF pressure without development of secondary overshoot.

**lection and Evaluation of Urinary Tract Antimicrobial Therapy**—Clair E. Cox, M.D., Winston-Salem, by invitation. The three-section exhibit displays those methods currently available for the selection and subsequent evaluation of antimicrobial therapy as it applies to infections of the urinary tract. Section one is devoted to the selection of antibiotic therapy; section two emphasizes the application of follow-up urine cultures; section three demonstrates the application of the above principles in a study of 50 patients.

**Spinal Anesthesia: Techniques and Applications: A Modern Approach**—Murray K. Rosenberg, M.D., Chicago, by invitation. The purpose of this exhibit is to present to the medical profession—especially the non-anesthesiologist—the reasons why spinal anesthesia, although not being extensively used at the present time, is the anesthetic of choice in many surgical procedures. The exhibit describes the accepted techniques of performing the spinal anesthetic as well as the principles of managing the patient during the operative and post-operative periods. It also presents the indications and contra-indications for this form of anesthesia. An attempt is made to try to counter the trend in medico-legal medicine which has limited the use of spinal anesthesia in modern times.

**Superficial Cervical Conization: A Disposable Office Device**—Bernard McDonald, M.D., Los Angeles. A new, disposable device for the detection of cervical cancer is introduced. It is designed for office use and is intended to bridge the diagnostic gap between the routine "Pap" smear and the hospital cold cone. The use of the instrument and results of the method are demonstrated.

**Thrombosis and Hyperactive Platelets in Primary Gout**—Gilbert H. Bluhm, M.D., Detroit, by invitation. The patient with gout appears to be significantly more susceptible to thrombotic complications before the age of 50 years. Decreased platelet survival has been reported previously in gouty patients. The coagulation profile in 25 gouty patients was essentially normal, but platelet differential counts with the electron microscope revealed abnormal surface activation. Our technique of platelet evaluation is described. Micrographs illustrating platelet changes as viewed by transmission and scanning electron microscopy are presented. Normal platelets were found to be activated by hyperuricemia. Some drugs used to reduce hyperuricemia were found also to directly inhibit platelet activation in patients with gout.

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VISIT THE

# TECHNICAL EXHIBITS

In the Arena and Grand Lobby  
Of the Anaheim Convention Center

March 13-16, 1971

9:00 a.m. to 5:00 p.m.



# WOMAN'S AUXILIARY

Forty-First Annual Convention

MARCH 14 to 17, 1971

Headquarters: Disneyland Hotel, Anaheim

Convention Chairman: Mrs. Frank Kendrick

Convention Co-Chairman: Mrs. Laurance Mosier

## REGISTRATION: Magnolia Mezzanine

Sunday, March 14—9:00 a.m. to 4:00 p.m.

Monday, March 15—8:00 a.m. to 4:00 p.m.

Tuesday, March 16—8:30 a.m. to Noon

## SATURDAY, MARCH 13—Pre-Convention

4:00 p.m.—Presentation of Mrs. Kenneth J. McNiece, Auxiliary President, to CMA House of Delegates, Anaheim Room, Convention Center. Doctors' wives are invited to attend.

## SUNDAY, MARCH 14

9:00 a.m.—Executive Committee Breakfast Meeting, President's Suite

1:30 p.m.—Pre-Convention Board Meeting, Sierra Tower Balboa Room

7:00 p.m.—Presidents' Reception, Magnolia Room

## MONDAY, MARCH 15

9:00 a.m.—Opening Session of House of Delegates, Embassy Room

12:00 noon—Salad luncheon served buffet style in Embassy Room

1:30 p.m.—Afternoon Session of House of Delegates, Embassy Room

6:30 p.m.—"Evening in Newport Beach." Shopping at Fashion Island, dinner afterwards at Bob Burns Restaurant

## TUESDAY, MARCH 16

9:00 a.m.—Final Session of House of Delegates, Embassy Room

12:30 p.m.—Presidents' Luncheon and Fashion Show, Magnolia Room

3:00 p.m.—Presentation of Mrs. John L. Gallagher, Incoming Auxiliary President, to the CMA House of Delegates, Anaheim Room, Convention Center

## WEDNESDAY, MARCH 17—Post-Convention

8:00 a.m.—Post-Convention Board of Directors meeting, Magnolia Room B

10:00 a.m.—Orientation Meeting, Magnolia Room B

## HOSPITALITY CENTER—Magnolia Room A

Sunday, March 14, 9:00 a.m. to 4 p.m.

Monday, March 15, 8:00 a.m. to 4 p.m.

Tuesday, March 16, 8:00 a.m. to 11 a.m.

INFORMATION BOOTH—Lobby of the Marina Tower



**MRS. KENNETH J. McNIECE**

*President*



**MRS. JOHN L. GALLAGHER**

*President-Elect*

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## House of Delegates

TOTAL DELEGATES (355)

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William F. Quinn, Los Angeles.....*Speaker, House of Delegates*  
Joseph F. Boyle, Los Angeles.....*Vice-Speaker, House of Delegates*  
Harold Kay, Oakland.....*Chairman of the Council*  
Helen B. Weyrauch, San Francisco.....*Secretary*  
Malcolm S. M. Watts, San Francisco.....*Editor*

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Thomas N. Elmendorf (1971).....*Eleventh District*  
Forest J. Grunigen (1971).....*Twelfth District*  
Charles J. Tupper (1973).....*Scientific Board Representative*

### ELECTED DELEGATES (282)

#### ALAMEDA-CONTRA COSTA (21)

##### Delegates

Anderson, Bruce M.  
Anderson, Conrad E.  
Buehler, John M.  
Davis, Aaron E.  
Davis, Velma L.  
Donald, William G.  
Eisenberg, Harold J.  
Goodman, Julien M.  
Griest, Elwood C.  
Hoskins, H. Dean  
Hudson, Charles B.  
Juil, Clement O.  
Kunkel, Peter  
Lewis, Gwilym B.  
Murphy, Joseph P.  
Neighbor, Jean E.  
Palmer, Rodney I.  
Powell, Oscar M.  
Purcell, Edward F.  
Richards, Dexter N.  
Rihn, Richard

##### Alternates

Adams, Richard Paul  
Adams, Robert  
Barber, Thomas E.  
Byers, Gilbert  
Cangello, Vincent W.  
Cherry, Donald W.  
Cook, Wallace H.  
Dooley, John D.  
Duffy, Charles C.  
Friesen, Howard  
Frost, Gordon  
Goetsch, Carl  
Hartzell, Walter J.  
Hauer, Samuel D.  
Kirk, Ralph  
Plaut, Eric A.  
Potter, Ronald R.  
Ross, Joseph  
Shapiro, Robert L.  
Upton, Albert L.  
Vickery, John E., Jr.

#### BUTTE-GLENN (2)

Murphy, Franklin L.  
Ritter, Dale W.

#### FORTY-FIRST (2)

#### FRESNO (5)

Ginsburg, H. M.  
Millar, Max  
Smith, Robb  
Snyder, L. J.  
Steinberg, Theodore

Hubbard, C. K.  
Sears, Adrian R. M.

DeFries, William  
Kass, Robert  
Packer, Benjamin  
Tostenson, N. E.  
Wilde, N. John

#### HUMBOLDT-DEL NORTE (2)

#### IMPERIAL (2)

#### INYO-MONO (2)

Jones, M. R.  
Sheldon, D. B.

##### Alternates

Eckert, Wade  
Knecht, E. E.

#### KERN (4)

Osell, L. N.  
Reese, Thomas V.  
Strongin, Seymour  
Vaughan, J. E.

Anderson, Gene  
Ardell, D. S.  
Clark, M. Marlin  
Spaulding, Keith W.

#### KINGS (2)

#### LASSEN-PLUMAS-MODOC-SIERRA (2)

#### LOS ANGELES (93)

Adams, Donald A.  
Alter, Marvin S.  
Amerongen, Frederick K.  
Andersen, George C.  
Anderson, Richard E.  
Aquila, S. J.  
Asher, Leonard M.  
Axelrod, Bernard  
Bailey, Wilbur  
Baker, Jack W.  
Bernstein, Harold  
Blood, William  
Bowen, Gordon T.  
Boyle, Joseph F.  
Breakstone, Gerald J.

Affley, Harry J., Jr.  
Alban, Seymour L.  
Alexakis, Peter  
Amar, Vincent F.  
Bergin, William F.  
Bergreen, Stanley W.  
Bradley, Gerald H.  
Brennan, James E.  
Bruckner, Sherman H.  
Carney, Padraig  
Condit, Leonard O.  
Covell, David G.  
Cronin, John F.  
Dashe, Alfred M.  
Davies, William D.



## Delegates

Brennan, John C.  
Briney, Allan K.  
Buehler, George S.  
Bullock, Lewis T.  
Cobb, Dudley M., Jr.  
Cope, Jerome A.  
Crumrine, Martin H.  
D'Orazio, Edward  
Dora, Robert M.  
Doyle, John B., Jr.  
Dukes, Robert W.  
Ellerbeck, Walter P.  
Elshire, H. Donel  
Evashwick, George  
Fields, Albert  
Fitch, Donald R.  
Ford, James H.  
Frank, William P.  
Freeman, Gordon L.  
Haschka, August J., Jr.  
Hill, Harry E.  
Horner, David B.  
Horowitz, Samuel  
Jones, Henry A.  
Kaemerle, Rudolph E.  
Ketcham, Burton E., Jr.  
Kiddie, Thomas  
Kugel, Arthur I.  
LaForge, William C.  
Lau, Michael W.  
Lefevre, Timothy M.  
MacInnis, Douglas N.  
Mailman, Richard H.  
May, Lewis H. V.  
Mazur, Murray H.  
McLaughlin, Henry M.  
Meine, Emile L.  
Miller, Richard D.  
Milliken, Ralph M.  
Morgan, Henry G.  
Murrieta, A. J., Jr.  
Neuenschwander, Robert S.  
Nishizawa, Akira  
Noguchi, Thomas T.  
Olch, David I.  
Parlour, Richard R.  
Penka, Ernest J.  
Penn, Sidney W.  
Pettit, Richard D.  
Pheasant, Homer  
Pollack, John V.  
Quinn, William F.  
Revere, Jack W.  
Richards, Melvin  
Roberts, James C., Jr.  
Rosenberg, Irving G.  
Sakaguchi, Sanbo S.  
Senseman, W. R.  
Shearer, S. K.  
Smith, Thayer A.  
Starr, Harvey E.  
Stauffer, Floyd R.  
Stragnell, Robert  
Sullivan, Richard A.  
Taw, Richard L.  
Trumbull, William E.  
Turrill, Fred L.  
Voight, Philip F.  
Walter, LeRoy E.  
Watson, Robert L., Jr.  
Weil, William S.  
Weiss, Murray J.  
Westerbeck, Charles W.  
Wiater, Edward J.  
Wunderlich, Edwin E.  
Zinn, Alexander N.  
Zinn, Willard J.

## MARIN (4)

Jaros, Duval  
Lee, John R.  
Strathairn, T. Scott  
White, A. H.

## MENDOCINO-LAKE (2)

Nicholson, Thomas A.  
Waring, William W.

## MERCED-MARIPOSA (2)

Anglin, John  
Faber, Dorian

## MONTEREY (3)

Hull, Osman H.  
Klinefelter, Robert P.  
Turner, Joseph E.

## NAPA (2)

Brignoli, Walter H.  
Ledwich, Thomas W.

## Alternates

Del Junco, Tirso  
Dickes, Richard E.  
Duemler, Louis P.  
Edwardes, Arthur F.  
Erickson, James F.  
Farfel, Beryl A.  
Fortier, John J.  
Freebairn, J. Richard  
Freidin, Morris  
Fritz, Samuel H.  
Gaal, Peter G.  
Goodwin, William E.  
Grant, Robert A.  
Greco, Donald J.  
Green, Jason I.  
Gregg, David W.  
Grobert, Marshall J.  
Gualtieri, Vincent  
Hardin, Byron  
Hoffman, Eugene F., Sr.  
Hoffman, Peter L.  
Japenga, Jack W.  
Kaminski, Kenneth L.  
Kaufmann, Bertram, Jr.  
Keller, Thomas B.  
Kelley, Walter W.  
Kern, William H.  
Killeen, Raymond N. F.  
Klein, E. Philip  
Kohler, Hugh F.  
Korn, Bernard J.  
Landon, Charles W.  
Lopez, Charles J.  
Lusche, John E.  
Martyn, Donald G.  
Massey, Ben D., Jr.  
McCaffery, James M.  
McCandless, Harrison C.  
McElwee, Charles B.  
Michels, Arthur G.  
Miller, Woodrow  
Moshein, Jack  
Murphy, Terrence J.  
Murray, Gregory C.  
Odou, Eugene R.  
Okie, Theodore B.  
Osher, Eugene M.  
Palmer, Robert H.  
Panish, Joel F.  
Picklesimer, James C.  
Rayman, Irving B.  
Redewill, Francis H., Jr.  
Rein, Harry  
Rodgers, Victor A.  
Romans, Robert M.  
Rosenkrans, Donald R., Jr.  
Rothenberg, Sanford F.  
Rubell, Earl B.  
Rudy, Norman E.  
Ryerson, F. Stuart  
Shirey, John K.  
Smiley, Douglas F.  
Smith, Laurence J.  
Stegeman, Walter  
Summers, L. F.  
Tashma, Albert  
Thom, John G.  
Titus, Edward D.  
Todd, William H.  
Tode, Jack C.  
Vogel, Philip J.  
Weiss, Benjamin J.  
White, John R.  
Wigton, John R.  
Wong, Thomas A.  
Woolley, Morton M.  
Wright, Carter R., Jr.

Alderson, Joseph  
Costanza, David  
Galeno, William  
Tavel, Frank

Browning, Donald  
Dailey, Frank

Kreps, Roland  
Soderstrom, Edwin

Eldredge, Eugene E.  
Elliott, Thomas S.  
Kandlbinder, A. F.

Ehrlich, Harry  
Murray, Dwight H., Jr.

## Delegates

### ORANGE (15)

Altman, Richard F.  
Andrews, Alan V.  
Ball, Dexter T.  
Carroll, Vincent P.  
Donaldson, A. Norton  
Geddes, David K.  
Gerrie, Wallace A.  
Graham, Ralph E.  
Kay, Fred M.  
Martin, Walter H.  
Mosier, Laurance A.  
Paul, Carl J.  
Schneider, Shirley M.  
Stonestreet, Marshall  
Thompson, Arthur F.

### PLACER-NEVADA (2)

Becker, Bruce A.  
Johnson, F. Harold

### RIVERSIDE (5)

Ivanoff, John C.  
Lyons, John C.  
Silver, Harrison E.  
Stone, H. H.  
Zweig, Robert M.

### SACRAMENTO (8)

Babich, John  
Cook, Orrin S.  
Farley, James O.  
Fong, William  
Martin, James  
O'Kane, Calvin  
Pope, Glenn A.  
Shaffrath, Max D.

### SAN BENITO (2)

Brooks, Fisk  
Currie, Norman

### SAN BERNARDINO (7)

Halberg, C. T.  
Hendrickson, M. A.  
Melone, Frank  
Miano, Ben D. A.  
Sprague, C. P.  
Sterling, Allen F.  
Wake, Donald K.

### SAN DIEGO (15)

Brumbaugh, Simon C., Jr.  
Feeney, Michael J.  
Hippen, Robert L.  
Hokr, William K.  
King, Ralph M.  
Kirtland, Howard B.  
Messenger, Harold M.  
Peabody, Homer D., Jr.  
Peck, J. Haddon A., Jr.  
Peck, Sam  
Plumb, Robert T.  
Rumsey, John M.  
Tancredi, Chester  
Tisdale, William K.  
Wells, John J.

### SAN FRANCISCO (20)

Baer, Charlotte C.  
Barrios, Xavier O.  
Bender, William T.  
Biskind, Gerson R.  
Cohn, Bradford  
Cole, Arthur H.  
Fullenlove, Tom M.  
Gibbons, Henry, III  
Herzog, George K., Jr.  
Jew, Jack  
Lee, Jane F.  
Pevehouse, Byron C.  
Pillsbury, Philip L.  
Rixford, Emmet L.  
Robinson, Saul J.  
Saunders, John B. deC. M.  
Schaffarzick, Ralph W.  
Schaupp, Willis C.  
Scholten, Paul  
Wayburn, Edgar

### SAN JOAQUIN (4)

Benn, James J.  
McNally, John T.  
Salter, Robert K.  
Williams, George J.

### SAN LUIS OBISPO (2)

Chambers, James R.  
Cletsoway, Richard W.

## Alternates

Bostick, Warren L.  
Bouchelle, McLemore  
Burrill, C. William  
Doyle, James R.  
Farter, John  
Grimes, Donald  
Higger, Harvey L.  
Kammerman, Richard F.  
Llewellyn, Gene A.  
McFarland, Philip H.  
Neu, Robert E.  
Plows, Charles W.  
Singer, Melville I.  
Voge, Lyle C.  
Wightman, Ardath H.

Anthony, William A.  
Sweeney, George H., Jr.

Borak, Peter J.  
Kinney, William  
Lansing, J. Dee  
Pitchford, Clyde A.  
Shumway, Ord L.

Bonser, Quentin  
Bramham, James  
Brown, Frank A.  
Janushkowsky, Alex  
O'Neal, Roy L.  
Quillinan, Robert  
Reilly, Philip J.  
Stanford, Roy

Quinn, Robert D.  
Telfer, James

Ballard, Ross L.  
Carmack, Charles  
Gillespie, James  
Harer, W. Benson, Jr.  
Jernigan, Shelby  
Judd, Richard  
Moseley, Wendell L.

Bartel, Robert M.  
Bishop, John A.  
Cowell, William E.  
Dill, Donald M.  
Elliott, Gladden V.  
Freeman, Gordon R.  
Gleason, Matthew C.  
Heard, Jerome L.  
Herrick, William C.  
Hindman, Robert E.  
Maloney, Basil W.  
Reck, Lawrence E.  
Shumacher, Alan E.  
Tanaka, Francis I.  
Tullis, Richard H.

Allen, David W.  
Bryan, John R.  
Carr, Lawrence B.  
Cook, Robert E.  
Driscoll, John A.  
Erskine, John M.  
Franzi, Antonin J.  
Gorney, Mark  
Hill, Frank deM.  
Jacobs, Herbert N.  
Kelley, Edward T.  
King, Charles D.  
Musser, Don C.  
Palmer, Richard F.  
Paver, Robert L.  
Sachs, David D.  
Solari, Rafael A.  
Wellington, Charles J.  
White, Laurens P.  
Williams, A. Justin

Clark, Stanley A.  
Shinn, William  
Talley, Robert  
Wass, Warren

Hughell, J. Edward  
Osibin, Willard S.

<i>Delegates</i>	<i>Alternates</i>	<i>Delegates</i>	<i>Alternates</i>
<b>SAN MATEO (7)</b> Hart, Ward L. Healy, Francis A. Hills, Oscar W. Lindsey, Howard W. Novak, Frank J. Rossiter, Stanford B. Thompson, William H.		<b>TULARE (2)</b> Goettle, James W. Lavers, George D.	McConnaughey, Hal D. Natzke, Richard
<b>SANTA BARBARA (5)</b> Blanchard, John P. McNiece, Kenneth J. Miles, Harold B. Rutten, R. John Ziemba, Joseph F.		<b>VENTURA (4)</b> Gstettenbauer, Joseph F. Hair, Charles M. Huff, W. Cloyce Rulfo, Henry J.	Colbern, Edwin C. Johnston, D. Gordon Riskin, Charles E. Stoutz, Henry L.
<b>SANTA CLARA (14)</b> Armstrong, Frederick S. Boice, Clyde L. English, Leo Fox, Leon P. Giansiracusa, Frank Grossman, Maurice Kaufman, S. Fred Lee, R. Hewlett Liston, Edward McCort, James J. O'Neill, Robert Rowles, Donald J. Scarborough, C. Gerald Zoglin, Stanton		<b>YOLO (2)</b> Wilson, B. Kent Young, Corbin	Dawkins, C. Edward Wisner, F. H.
<b>SANTA CRUZ (3)</b> DePuy, James L. Jones, Robert W. Nelson, Carl		<b>YUBA-SUTTER-COLUSA (2)</b>	
<b>SHASTA-TRINITY (2)</b>		<b>EX-OFFICIO SCIENTIFIC BOARD (18)</b>	
<b>SISKIYOU (2)</b>		Bergman, R. Theodore Brockman, Seymour J. Chope, Harold D. Demorest, Byron H. Dillon, John B. Donnell, George N. Gonda, Thomas A. Halter, Bert L. Hibbard, Lester T. Hockwald, Robert S. Holden, Herbert A. Hughes, Alfred Kaye, Ronald L. Maibach, Howard I. Meyelco, Leo N. Stein, Justin J. Tupper, C. John Wood, David A.	Bittner, Donald L. Cailliet, Rene Carson, Merl J. Cobb, Dudley, Jr. Connolly, John E. Gross, George A. Harris, M. Robert Hippen, Robert L. Hogan, Michael J. Jones, S. Austin Monsen, David C. G. Opfell, Richard W. Richards, Victor Rolf, Bruce Stevens, Leyland E. Swift, Sherrod C.
<b>SOLANO (2)</b> Gullock, Alvin H. Vincent, Keith E.		<b>EX-OFFICIO PAST PRESIDENTS (23)</b>	
<b>SONOMA (3)</b> Anderson, Raymond C. Dunn, William J. Lones, Frank E.		Peers, Robert A. ....1935 Molony, William R., Sr. ....1942 Schaupp, Karl L., Sr. ....1943 Cline, John W. ....1947 Askey, E. Vincent. ....1948 Cass, Donald ....1950 MacLean, H. Gordon. ....1951 Green, John W. ....1953 Morrison, Arlo A. ....1954 Shipman, Sidney J. ....1955 MacDonald, Frank A. ....1957 West, Francis E. ....1958	Reynolds, T. Eric. ....1959 Foster, Paul D. ....1960 Bostick, Warren L. ....1961 Wheeler, Omer W. ....1962 Sherman, Samuel R. ....1963 Doyle, James C. ....1964 Teall, Ralph ....1965 MacLaggan, James C. ....1966 Morrison, John G. ....1967 Todd, Malcolm C. ....1968 Miller, Albert G. ....1969
<b>STANISLAUS (3)</b> Nelson, William New, David J. Purvis, Robert		<b>EX-OFFICIO HONORARY PAST PRESIDENTS (2)</b>	
<b>TEHAMA (2)</b>		Murray, Dwight H. Wilbur, Dwight L.	



# House of Delegates • 1971 Annual Session

## AGENDA

Anaheim Room, Anaheim Convention Center

Speaker.....William F. Quinn, Los Angeles  
Vice-Speaker.....Joseph F. Boyle, Los Angeles  
Secretary.....Helen B. Weyrauch, San Francisco

**FIRST MEETING, Saturday, March 13, 1971**

**REGISTRATION—3 p.m.**

**MEETING STARTS—4 p.m. SHARP**

1. Call to order.
2. Announcement of Reference Committees and Miscellaneous Announcements.
  - (a) Committee on Credentials. (Delegates must register with the Committee.)
  - (b) Reference Committee on Community and Environmental Health. (Reference Committee A.)
  - (c) Reference Committee on Government Medical Programs. (Reference Committee B.)
  - (d) Reference Committee on Medical Economics, Insurance and Prepayment. (Reference Committee C.)
  - (e) Reference Committee on Scientific and Educational Activities. (Reference Committee D.)
  - (f) Reference Committee on Public and Professional Relations. (Reference Committee E.)
  - (g) Reference Committee on Finance. (Reference Committee F.)
  - (h) Reference Committee on Constitution and By-laws. (Reference Committee G.)
  - (i) Reference Committee on California Blue Shield. (Reference Committee H.)
3. Honored Guests.
  - (a) Fifty-year members.
  - (b) Past Presidents.
  - (c) Allied Health Groups.
  - (d) SAMA Students.
4. Report of Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of the Woman's Auxiliary to the CMA—Mrs. Kenneth J. McNiece.
6. Address by President—Ralph W. Burnett.
7. Report of the President—Ralph W. Burnett.
8. Report of the President-Elect—Roberta F. Fenlon.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—William F. Quinn and Joseph F. Boyle.
10. Report of the Trustees of the California Medical Association—Ralph W. Burnett.
11. Report of Physicians' Benevolence Fund, Inc.—Ralph W. Burnett.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director—Robert L. Thomas.
15. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber.
16. Report of the Executive Committee—Ralph W. Burnett.
17. Report of the Council—Harold Kay, Chairman.
18. Report of California Blue Shield Trustees—Carl E. Anderson, Chairman of the Board of Trustees.
19. Reports of Commissions.
  - (a) Commission on Medical Services — Arthur F. Howard, Fresno.
  - (b) Commission on Public Agencies — Joseph P. O'Connor, Pasadena.
  - (c) Commission on Community Health Services—Marvin J. Shapiro, Encino.
  - (d) Commission on Communications — James C. MacLaggan, San Diego.
  - (e) Commission on Professional Welfare — George K. Herzog, Jr., San Francisco.
  - (f) Judicial Commission — W. Philip Corr, Riverside.
  - (g) Commission on Allied Health Professions and Services — Lewis T. Bullock, Los Angeles.
  - (h) Commission on Hospital Affairs — Joseph W. Telford, San Diego.
  - (i) Commission on Legislation — Malcolm C. Todd, Long Beach.
  - (j) Scientific Board — C. John Tupper, Davis.
20. Reports of Other Committees.
  - (a) Bureau of Research and Planning — Henry V. Eastman, Tustin.
  - (b) Role of Medicine in Society — Malcolm S. M. Watts, San Francisco.
  - (c) Organizational Review and Planning — E. Kash Rose, Napa.
  - (d) Finance Committee — Henry Eastman, Tustin.
  - (e) Medical Executives Conference — Norman A. Brown, Sonoma.
  - (f) Delegates to the AMA — Samuel R. Sherman, San Francisco.
21. Old and unfinished business.
22. New Business.
23. Adjournment.

### CALPAC REPORTS

Immediately Following the Opening Session  
of the CMA House of Delegates

SECOND MEETING, Tuesday, March 16, 1971, at 1:30 p.m.

(To be recessed and reconvened at 9:00 a.m., Wednesday, March 17.)

ORDER OF BUSINESS

1. Call to order.
  2. Supplemental report of Credentials Committee—Roll Call.
  3. Introduction of President-Elect of Woman's Auxiliary — Mrs. John L. Gallagher.
  4. Address by President-Elect — Roberta F. Fenlon.
  5. Secretary's announcement of Council's selection of time and place for the 1972 Annual Session.
  6. Election of Officers:
    - (a) President-Elect.
    - (b) Speaker.
    - (c) Vice-Speaker.
    - (d) Councilors (three-year terms):
      - (1) Second District — Nicholas P. Krikes, San Bernardino (term expiring).  
Second District — Inyo, Mono, Riverside and San Bernardino Counties.
      - (2) Fourth District — Office No. 1 — M. M. Haskell, Long Beach, (term expiring).
      - (3) Fourth District — Office No. 4 — Lewis T. Bullock, Los Angeles, (term expiring).
      - (4) Fourth District — Office No. 7 — George C. Andersen, Hermosa Beach, (term expiring).  
Fourth District — Los Angeles County.
      - (5) Seventh District — Office No. 2 — John T. Saids, San Mateo, (term expiring).  
Seventh District — Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz Counties.
      - (6) Eleventh District — Thomas N. Elmendorf, Willows, (term expiring).  
Eleventh District — Alpine, Butte, Colusa, El Dorado, Glenn, Lassen, Modoc, Nevada, Placer, Plumas, Sacramento, Shasta, Sierra, Siskiyou, Sutter, Tehama, Trinity, Yolo and Yuba Counties.
    - (7) Scientific Board Representative—C. John Tupper, Davis.
  - (e) Delegates to the American Medical Association (Delegates and Alternates to the American Medical Association are elected for terms of two calendar years. The Delegates and Alternates to be elected at this meeting will serve for two calendar years starting January 1, 1972, except as otherwise noted.)
    - (1) Emmet Rixford, San Francisco (term expiring).
    - (2) Francis E. West, San Diego (term expiring).
    - (3) Samuel R. Sherman, San Francisco (term expiring).
    - (4) Albert G. Miller, San Mateo (term expiring).
    - (5) John M. Rumsey, San Diego (term expiring).
    - (6) Eugene F. Hoffman, Los Angeles (term expiring).
    - (7) Warren L. Bostick, Los Angeles (term expiring).
    - (8) Vincent P. Carroll, Laguna Beach (term expiring).
    - (9) Ralph C. Teall, Sacramento (term expiring).
    - (10) Dudley M. Cobb, Los Angeles (term expiring).
    - (11) Wilbur G. Rogers, Glendale (term expiring).
    - (12) Charles B. Hudson, Oakland (term expiring).
  - (f) Alternates to the American Medical Association: (terms of all incumbents expiring. All offices for two year terms starting January 1, 1972, except as otherwise noted.)
    - (1) Ralph W. Schaffarzick, San Francisco (alternate to Emmet Rixford).
    - (2) Laurance A. Mosier, Garden Grove (alternate to Francis E. West).
    - (3) George K. Herzog, Jr., San Francisco (alternate to Samuel R. Sherman).
    - (4) Thomas Elmendorf, Willows (alternate to Albert G. Miller).
    - (5) John V. Pollack, Los Angeles (alternate to John M. Rumsey).
    - (6) Joseph F. Boyle, Los Angeles (alternate to Eugene F. Hoffman).
    - (7) Walter H. Brignoli, St. Helena (alternate to Warren L. Bostick).
    - (8) Herbert A. Holden, San Leandro (alternate to Vincent P. Carroll).
    - (9) Arthur F. Howard, Fresno, (alternate to Ralph C. Teall).
    - (10) Gregory Murray, Los Angeles, (alternate to Dudley M. Cobb).
    - (11) Ben D. A. Miano, San Bernardino (alternate to Wilbur G. Rogers).
    - (12) Robert L. Watson, Jr., Los Angeles (alternate to Charles B. Hudson).
7. Election of California Blue Shield Trustees (three-year terms):

Report of CMA Council as Nominating Committee. Incumbents, terms expiring:

Richard F. Altman, Newport Beach  
Burt Davis, Palo Alto  
Donald R. Fitch, Glendale  
Bert L. Halter, San Francisco
8. Announcement by Secretary.

Council's nominations of members of Commissions and Committees. (For approval by the House of Delegates).
9. Reports of Reference Committees:
  - (a) Report of Reference Committee A on Community and Environmental Health.
  - (b) Report of Reference Committee B on Government Medical Programs.
  - (c) Report of Reference Committee C on Medical Economics, Insurance and Prepayment.
  - (d) Report of Reference Committee D on Scientific and Educational Activities.
  - (e) Report of Reference Committee E on Public and Professional Relations.
  - (f) Report of Reference Committee F on Finance.
  - (g) Report of Reference Committee G on Constitution and Bylaws.
  - (h) Report of Reference Committee H on California Blue Shield.



10. Unfinished Business.
11. New Business.
12. Presentation of Officers:  
President — Presentation of Plaque to President Ralph W. Burnett.  
President-Elect.

Speaker.  
Vice-Speaker.

13. Approval of Minutes. (Committee to edit.)
14. Adjournment.

WILLIAM F. QUINN, *Speaker*  
HELEN B. WEYRAUCH, *Secretary*

## Constitutional Amendment

### FOR ACTION IN 1971

Three Constitutional amendments were introduced in the 1970 House of Delegates. One amendment was withdrawn by the author. Under the terms of the Constitution, the remaining two amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

### COMPOSITION OF COUNCIL ARTICLE III, SECTION 9

Constitutional Amendment 1-70      Committee G  
Introduced by: Simon Brumbaugh, M.D.  
Representing: San Diego County Medical Society

WHEREAS, the growth in medical population in California has continued to increase at a rapid rate; and

WHEREAS, the size of the CMA Council has increased with the size of the medical population; and

WHEREAS, the efficiency of the Council decreases with increase in size; and

WHEREAS, the expense of maintaining the Council increases with size; now, therefore, be it

*Resolved:* That Article III, Section 9 of the Constitution of this Association be amended by deleting the figures in parentheses and adding the figures in italics, so that this Section will read as follows:

"The Council shall consist of:

(a) Elected councilors from the councilor districts set forth in Section 10. Each councilor district shall be entitled to elect one councilor for each (1,000) *1,500* active members, or major fraction thereof, according to its membership as of the first day of September of the preceding year; provided, that each councilor district shall be entitled to a minimum of one councilor"; and be it further

*Resolved:* That the Council through its committees review the ratio of membership to councilor representation each five years; and be it further

*Resolved:* That the Council be empowered to change this ratio after such review each five years as necessary for efficiency and economy.

### COMPONENT MEDICAL STUDENT SOCIETY ARTICLE I, SECTION 4, AND ARTICLE III, SECTION 7(a)

Constitutional Amendment 2-70      Committee G  
Introduced by E. Kash Rose, M.D.

WHEREAS, medical students of Schools of Medicine in California have demonstrated a desire to be increasingly involved in the activities of the medical profession in California generally, and the activities of the California Medical Association specifically; and,

WHEREAS, such involvement of medical students in these activities may offer significant and mutual benefits to the California Medical Association and to the medical students; and,

WHEREAS, this involvement and the anticipated mutual benefits might best be encouraged and achieved through the formation of a new component society to be known as the "Component Medical Student Society"; and,

WHEREAS, the California Medical Association will be evaluating this and other proposals during the coming year; and,

WHEREAS, if this evaluation suggests that the California Medical Association form a "Component Medical Student Society," certain amendments to the Constitution will be necessary; and

WHEREAS, the anticipatory introduction at this time of such necessary amendments to the Constitution will serve the next House of Delegates should it wish to charter a "Component Medical Student Society" by satisfying the "one year time requirement" as specified in Article VIII, Section 3 of the Constitution; therefore, be it

*Resolved:* That the Constitution of this Association be amended as follows:

1. That Article I, Section 4 of the Constitution of this Association be amended by deleting the word in parentheses and by adding the words in italics, so that this section shall read:

"Component societies include all county medical societies, which may cover one or more counties, (or) any established component district of at least 300 members of a county society which has exercised option to withdraw from that county society and set up a separate component society, heretofore or hereafter, chartered by this Association, *or a Component Medical Student Society consisting of bona fide medical students at accredited Schools of Medicine in California.*"

2. That Article III, Section 7(a) of the Constitution of this Association be amended by deleting the word in parentheses and by adding the words in italics, so that this section shall read:

"(a) The House of Delegates shall issue charters to medical societies of any county, any component society of at least 300 members which has exercised its option to become autonomous, (or) to any group of counties deemed eligible which have made proper application therefor *or to a Component Medical Student Society.*"

Reports of officers, commissions and committees of the California Medical Association, together with the following audited financial statements for the fiscal year ended June 30, 1970, are printed in the Annual Report Bulletin, which is distributed to Delegates and Alternates at the meeting of the

House of Delegates. The Bulletin is also available to any member of the Association on request directed to Robert L. Thomas, Executive Director, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

## FINANCIAL REPORTS

### CALIFORNIA MEDICAL ASSOCIATION AND TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

(See pages 42-46)

#### REPORT OF

#### *Certified Public Accountants*

#### CALIFORNIA MEDICAL ASSOCIATION:

We have examined the balance sheets of California Medical Association and Trustees of California Medical Association at June 30, 1970, and the related statements of income and expenses for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial position of California Medical Association and Trustees of California Medical Association at June 30, 1970, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

JOHN F. FORBES & COMPANY

San Francisco, California  
August 18, 1970



**CALIFORNIA  
MEDICAL  
ASSOCIATION**

(A Nonprofit Association)

**Balance Sheet,  
June 30, 1970  
and 1969,  
and Comparison**

	JUNE 30		Increase (Decrease)
	1970	1969	
ASSETS			
CASH .....	\$ 62,426	\$ 62,425	\$ 1
UNITED STATES TREASURY BILLS, AT COST.....	1,074,032	1,081,894	(7,862)
ACCOUNTS RECEIVABLE, NET.....	115,476	86,041	29,435
ACCRUED INTEREST .....	11,586	6,297	5,289
NOTES RECEIVABLE:			
Central California Blood Bank .....	71,000	71,000	
Other .....	2,400	3,200	(800)
Total notes receivable .....	73,400	74,200	(800)
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1) .....	19,142	17,530	1,612
Insurance .....	4,114	2,880	1,234
Deposits .....	4,161	4,383	(222)
Other .....	7,459	3,424	4,035
Total prepaid expenses and other assets....	34,876	28,217	6,659
OFFICE FURNITURE AND EQUIPMENT (Note 2) .....	44,280	46,375	(2,095)
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note, with interest at 4% per year .....	125,000	125,000	
Account receivable .....		3,140	(3,140)
	125,000	128,140	(3,140)
Accounts receivable:			
Six Ninety Three Sutter Publications, Inc. ....	5,498		5,498
California Medical Education and Research Foundation, Inc. ....	7,665	22,843	(15,178)
Other .....	4,424	1,331	3,093
Total notes and accounts receivable, affiliated organizations .....	142,587	152,314	(9,727)
	<u>\$1,558,663</u>	<u>\$1,537,763</u>	<u>\$ 20,900</u>
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Association .....	\$ 80,430	\$ 23,310	\$ 57,120
American Medical Education Foundation .....		27,865	(27,865)
Other .....	38,028	62,556	(24,528)
Total accounts payable .....	118,458	113,731	4,727
DUE TO AFFILIATED ORGANIZATIONS:			
Physicians' Benevolence Fund .....	22,565	22,441	124
Six Ninety Three Sutter Publications, Inc. ....		3,379	(3,379)
Total due to affiliated organizations .....	22,565	25,820	(3,255)
INTERAGENCY COUNCIL ON DRUG ABUSE.....	2,378		2,378
DEFERRED INCOME:			
Dues and subscriptions applicable to the succeeding fiscal year .....	995,691	962,110	33,581
Other .....	3,480	417	3,063
Total deferred income .....	999,171	962,527	36,644
Total liabilities .....	1,142,572	1,102,078	40,494
EXCESS OF ASSETS OVER LIABILITIES (Note 3) .....	416,091	435,685	(19,594)
	<u>\$1,558,663</u>	<u>\$1,537,763</u>	<u>\$ 20,900</u>

See notes to financial statements.

**CALIFORNIA  
MEDICAL  
ASSOCIATION**

	JUNE 30		Increase (Decrease)
	1970	1969	
UNRESTRICTED:			
Balance, beginning of year	\$276,747	\$233,531	\$ 43,216
Excess of income over expenses for the year	5,406	86,433	(81,027)
Transfer to restricted	2,703	43,217	(40,514)
	<u>2,703</u>	<u>43,216</u>	<u>(40,513)</u>
Total	279,450	276,747	2,703
Contribution toward Bond Proposition One, not budgeted	25,000		25,000
Balance, end of year	<u>254,450</u>	<u>276,747</u>	<u>(22,297)</u>
RESTRICTED AS TO USE (Note 4):			
Balance, beginning of year	158,938	115,721	43,217
Transfer from excess of income over expenses	2,703	43,217	(40,514)
Balance, end of year	<u>161,641</u>	<u>158,938</u>	<u>2,703</u>
EXCESS OF ASSETS OVER LIABILITIES	\$416,091	\$435,685	\$(19,594)

See notes to financial statements.

**Excess of Assets  
Over Liabilities  
June 30, 1970  
and 1969, and  
Comparison**

<b>INCOME:</b>			
Membership dues, less portion allocated to subscriptions to CALIFORNIA MEDICINE	\$1,905,562	\$1,894,894	\$ 10,668
Booth rentals at Annual Session	42,051	39,930	2,121
Fees, postgraduate courses	17,362	19,690	(2,328)
Fee for collection of American Medical Association dues	15,269	15,688	(419)
Interest earned	54,926	55,114	(188)
Other	891	2,529	(1,638)
Total income	<u>2,036,061</u>	<u>2,027,845</u>	<u>8,216</u>
<b>EXPENSES:</b>			
Physicians' Services and Programs	324,808	290,106	34,702
Divisional Programs	1,280,078	1,266,056	14,022
General expenses	318,027	293,085	24,942
	<u>1,922,913</u>	<u>1,849,247</u>	<u>73,666</u>
Contributions	50,565	78,306	(27,741)
Excess of expenses over income—CALIFORNIA MEDICINE	57,177	13,859	43,318
Total	<u>2,030,655</u>	<u>1,941,412</u>	<u>89,243</u>
<b>EXCESS OF INCOME OVER EXPENDITURES</b>	<u>\$ 5,406</u>	<u>\$ 86,433</u>	<u>\$(81,027)</u>

See notes to financial statements.

**Statement of Income  
and Expenses  
Years Ended  
June 30, 1970  
and 1969,  
and Comparison**



**TRUSTEES OF THE  
CALIFORNIA  
MEDICAL  
ASSOCIATION**  
(A Nonprofit Corporation)

Balance Sheet,  
June 30, 1970  
and 1969, and  
Comparison

	JUNE 30		Increase (Decrease)
	1970	1969	
ASSETS			
CASH	\$ 7,020	\$ 46,058	\$(39,038)
INVESTMENTS IN UNITED STATES TREASURY OBLIGATIONS, AT COST:			
Bonds	1,036,000	1,119,152	(83,152)
Bills (maturing within 6 months)	156,269		156,269
Total investments in United States Treasury obligations	1,192,269	1,119,152	73,117
ACCRUED INTEREST	2,795	2,119	676
ACCOUNTS RECEIVABLE		795	(795)
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST:			
Pacific Magnetic Tape Co. (Note 5)	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
PROPERTIES, AT COST (Note 6):			
Buildings and improvements	407,303	406,805	498
Carpets, installation, and other	19,521	19,026	495
	426,824	425,831	993
Less accumulated depreciation	139,500	118,631	20,869
	287,324	307,200	(19,876)
Land	180,217	180,217	
Properties, at cost, net	467,541	487,417	(19,876)
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE (Note 7)	56,749	51,391	5,358
ACCRUED REAL ESTATE TAXES (contra)	24,000	23,000	1,000
PREPAID INSURANCE AND OTHER EXPENSES	1,806	1,086	720
	<u>\$1,762,181</u>	<u>\$1,741,019</u>	<u>\$ 21,162</u>
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
Audio-Digest Foundation	\$ 2,930		\$ 2,930
California Medical Association	632	\$ 3,140	(2,508)
Interest and accrued expenses	663	3,499	(2,836)
Total accounts payable and accrued expenses	4,225	6,639	(2,414)
ACCRUED REAL ESTATE TAXES PAYABLE (contra)	24,000	23,000	1,000
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000	125,000	
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of \$2,506, includ- ing interest at 4¼% per year, to March 1, 1973) (Note 6)	23,211	32,014	(8,803)
Total notes payable	148,211	157,014	(8,803)
TRUST FUNDS (Note 7)	161,789	151,387	10,402
DEFERRED INCOME	785	760	25
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Balance, beginning of year	1,402,219	1,380,214	22,005
Excess of income over expenses for the year	20,952	22,005	(1,053)
Balance, end of year	<u>1,423,171</u>	<u>1,402,219</u>	<u>20,952</u>
	<u>\$1,762,181</u>	<u>\$1,741,019</u>	<u>\$ 21,162</u>

See notes to financial statements.

Statement of Income  
and Expenses  
Years Ended  
June 30, 1970  
and 1969, and  
Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)
	1970	1969	
INCOME:			
Net income (loss) from rental properties .....	\$(3,135)	\$ 3,650	\$(6,785)
Interest on United States Treasury obligations .....	33,831	29,000	4,831
Dividends—Pacific Magnetic Tape Equipment Co. ....	3,600		3,600
Net gains on sale of United States Treasury obligations .....	941		941
	<u>35,237</u>	<u>32,650</u>	<u>2,587</u>
EXPENSES (other than property)—			
Professional fees and insurance .....	4,793	4,090	703
	<u>30,444</u>	<u>28,560</u>	<u>1,884</u>
OTHER CHARGES—PROVISION FOR RETIREMENT OR OTHER BENEFITS OF EMPLOYEES OF AN AFFILIATED ORGANIZATION .....			
	9,492	6,555	2,937
EXCESS OF INCOME OVER EXPENSES FOR THE YEAR .....	<u>\$20,952</u>	<u>\$22,005</u>	<u>\$(1,053)</u>

See notes to financial statements.

## NOTE:

## 1. EMPLOYEE PENSION PLANS

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees which resulted in an additional liability of \$62,734. This liability is being amortized over 20 years from January 1, 1966. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Because the current service benefits and all of the benefits for retired employees have already been purchased under the contract, there is a liability only for the unfunded value of vested benefits. This liability amounted to \$9,254 on January 1, 1970. This amount is not recorded on the books of the Association nor included in the accompanying balance sheet.

The pension expense for the year was \$41,412. This expense is determined by the underwriter each year, and may vary, depending on new qualifying employees, and credits arising from qualifying employees leaving the Association.

## 2. OFFICE FURNITURE AND EQUIPMENT—CALIFORNIA MEDICAL ASSOCIATION

Acquisitions prior to July 1, 1966 are carried at a nominal amount of \$1. At May 13, 1966, the firm of Marshall and Stevens, appraisers, estimated that the sound value of assets then owned was \$104,415. Assets acquired after July 1, 1966, are summarized as follows:

	Cost	Depreciation or Amortization
Office furniture and equipment:		
Owned July 1, 1969 .....	\$61,492	\$16,993
Purchased during the current year .....	10,135	
Provision for the current year .....		11,046
	<u>71,627</u>	<u>28,039</u>
Leasehold improvements, Sacramento office:		
Cost .....	3,357	
Amortization .....		2,665
	<u>\$74,984</u>	<u>\$30,704</u>
Net book value .....	<u>\$44,280</u>	

## 3. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	JUNE 30		Increase
	1970	1969	
California Medical Association:			
Restricted as to use .....	\$ 161,641	\$ 158,938	\$ 2,703
Unrestricted .....	254,450	276,747	(22,297)
	<u>416,091</u>	<u>435,685</u>	<u>(19,594)</u>
Trustees of the California Medical Association .....	1,423,171	1,402,219	20,952
	<u>\$1,839,262</u>	<u>\$1,837,904</u>	<u>\$ 1,358</u>

The combined net worth at June 30, 1970 shown in the summary above does not include the following items:

## California Medical Association:

Excess of the appraised value of furniture and office equipment acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value, approximately .....

\$ 62,200

Trustees of the California Medical Association—Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Co., based on that company's unaudited balance sheet at June 26, 1970 .....

54,832

\$117,032

## 4. EXCESS OF ASSETS OVER LIABILITIES—RESTRICTED AS TO USE

The budget for the fiscal year ended June 30, 1968, as approved by the Council, authorized the segregation of a portion of the excess of income over expenses in the amount of \$115,721, leaving the remainder available for possible current requirements. For the fiscal year ended June 30, 1970, the amount of \$2,703 was added to the restricted balance. This addition represents one-half of the excess of income over expenses for this year.

## 5. WHOLLY-OWNED SUBSIDIARY OF TRUSTEES

The Trustees of the California Medical Association own all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation.

CALIFORNIA MEDICAL  
ASSOCIATION AND  
TRUSTEES OF THE  
CALIFORNIA MEDICAL  
ASSOCIATION

Notes to  
Financial Statements,  
June 30, 1970



## 6. PROPERTIES

The properties held by the Trustees of the California Medical Association are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Buildings and improvements .....	\$329,413	\$ 77,889	\$407,302
Carpets, installation, and other .....	18,852	670	19,522
	<u>348,265</u>	<u>78,559</u>	<u>426,824</u>
Less accumulated depreciation .....	124,952	14,548	139,500
	<u>223,313</u>	<u>64,011</u>	<u>287,324</u>
Land .....	87,400	92,817	180,217
	<u>\$310,713</u>	<u>\$156,828</u>	<u>\$467,541</u>

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company as collateral for a note with a balance of \$23,211 at June 30, 1970.

## 7. TRUST FUNDS

These funds are summarized as follows:

For Mr. and Mrs. Ben H. Read .....	\$ 66,000
Morris Herzstein Bequest .....	21,190
Life insurance retirement plan for legal counsel .....	56,749
Deferred compensation .....	17,850
	<u>\$161,789</u>

The portion of the Trust Funds applicable to the retirement or similar benefit to Mr. and Mrs. Ben H. Read, has not been segregated from other assets of the corporation as provided by the bylaws, as such funds are presently invested in United States Treasury securities of indivisible denominations.

The life insurance retirement plan for legal counsel is offset by the cash surrender value of a life insurance policy.

## 8. LITIGATION

California Medical Association is one of many defendants in an antitrust suit now pending in the U.S. District Court in San Francisco, California. The plaintiff seeks both an injunction and monetary damages in an aggregate amount of \$24,000,000. Counsel for the Association have stated that notwithstanding a careful examination of all of the facts for several months, they have found no evidence whatsoever that the plaintiff's claims against any of the defendants have any merit.

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# BOOKS RECEIVED

*Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

**HERNIA REPAIR WITHOUT DISABILITY—A Surgical Atlas Illustrating the Anatomy, Technique, and Physiologic Rationale of the "one day" hernia**—Irving L. Lichtenstein, M.D., Fellow; American College of Surgeons, International College of Surgeons, and American Association for the Advancement of Science; Diplomate; American Board of Surgery, Pan American Medical Association, and National Board of Medical Examiners; Associate, World Medical Association. C.V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1970. 210 pages, with 113 drawings by Daniel C. Garcia, B.F.A., \$26.50.

**THE PROBLEM-ORIENTED PRIVATE PRACTICE OF MEDICINE—A System for Comprehensive Health Care**—John C. Bjorn, M.D., and Harold D. Cross, M.D., Modern Hospital Press, McGraw-Hill Publications Co., 1050 Merchandise Mart, Chicago, Ill. (60654), 1970. 146 pages, \$4.95.

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**RECONSTRUCTIVE SURGERY OF THE MIDDLE EAR**—Adolph Wolfman, M.D., Attending Physician in Otolaryngology; Brooklyn Eye and Ear Hospital, Kings County Hospital, Brooklyn Jewish Hospital, New York Polyclinic Hospital, Brooklyn, and State University of New York (Downstate Medical Center); Illustrations by Lou Barlow. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 184 pages, \$25.00.

**A SYNOPSIS OF PHARMACOLOGY—Second Edition**—V.C. Sutherland, Ph.D., Professor of Pharmacology, University of California, San Francisco. W.B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 720 pages, \$10.75.

**WORLD DIALOGUE ON ALCOHOL AND DRUG DEPENDENCE**—Edited by Elizabeth D. Whitney. Beacon Press, 25 Beacon St., Boston, Mass. (02108), 1970. 400 pages, \$12.50.

**VITAMIN C AND THE COMMON COLD**—Linus Pauling. W. H. Freeman and Company, 660 Market Street, San Francisco, Ca. (94104), 1970. 122 pages, \$3.95 clothbound, \$1.95 paperbound.

**A CELEBRATION OF LAUGHTER**—Edited by Werner M. Mendel, M.D., Department of Psychiatry, University of Southern California, Los Angeles. Mara Books, 2840 West Rowena Avenue, Los Angeles, Ca. (90039), 1970. 189 pages, \$4.95.

**CLINICAL OBSTETRICS AND GYNECOLOGY—Volume 13, Number 2—Sepsis in Obstetrics**—Edited by Bernardo A. G. Santamarina, M.D.; **Dysfunctional Uterine Bleeding**—Edited by Edward E. Wallach, M.D. Harper & Row, Publishers, Inc., 49 East 33 Street, New York, N.Y. (10016), 1970. Published Quarterly, by Subscription Only, \$22.00 per Year.

**THE CLINICAL RECOGNITION OF CONGENITAL HEART DISEASE**—Joseph K. Perloff, M.D., Professor of Medicine, Chief Consultant in Pediatric Cardiology, and Lecturer in Physiology and Biophysics, Georgetown University School of Medicine, Washington, D.C.; Consultant, Veteran's Administration Hospital, Washington, D.C.; National Heart and Lung Institute, Bethesda, and Hospital for Sick Children, Washington, D.C.

**HEALERS IN UNIFORM**—Edward Edelson. Doubleday and Company, Inc., 277 Park Avenue, New York, N.Y. (10017), 1971. 184 pages, \$3.95.

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# Recent Advances in the Diagnosis and Treatment of Pemphigus

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- *Immunofluorescent techniques offer considerable promise in facilitating the diagnosis of pemphigus and other bullous diseases and also have provided a means for further investigative studies of these diseases. The immunofluorescent findings have in part stimulated the use of immunosuppressive agents in the management of pemphigus. Their exact status is still undetermined but early experience appears favorable.*

THE DEMONSTRATION OF ANTIBODIES directed against the intercellular substance of stratified squamous epithelium by Beutner and Jordon<sup>1</sup> in the serum of patients with pemphigus vulgaris by the indirect immunofluorescent staining technique has stimulated a renewed interest in the pathophysiology of pemphigus and other chronic bullous diseases. It has also provided a rational basis for immunosuppressive agents in the management of these recalcitrant diseases.

The term *pemphigus* (blister) has been applied in the past to a variety of cutaneous syndromes in which vesicle and bulla formation is characteristic. True pemphigus, however, is now considered to be a disease affecting principally the epidermis and mucous membranes of man<sup>2,3</sup> and is currently classified into four types. These are pemphigus vulgaris, pemphigus vegetans,

pemphigus foliaceus, and pemphigus erythematous. The still disputed primary changes which occur within cells of the epidermis adversely affect cohesive forces between these cells and eventually lead to breaking of intercellular bridges. This clinically results in development of vesicles and bullae which early rupture leaving large denuded areas with little tendency to heal. These bullae characteristically form intra-epidermally above the basal cell layer (Figure 1) in pemphigus vulgaris and within or below the granular layer in pemphigus foliaceus. Partially degenerated epidermal cells appearing spherical, hyperchromatic, with a homogenous cytoplasm and swollen nucleus may be observed singly and in clusters free in the fluid content (Figure 2).

## Clinical Classification

Pemphigus vulgaris is characterized by bullae arising on normal appearing skin. They are flaccid from the beginning and show little tendency

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<sup>3</sup>Reprint requests to: Division of Dermatology, Department of Medicine, University of California, Los Angeles, Center for the Health Sciences, Los Angeles 90024 (Dr. V. D. Newcomer).



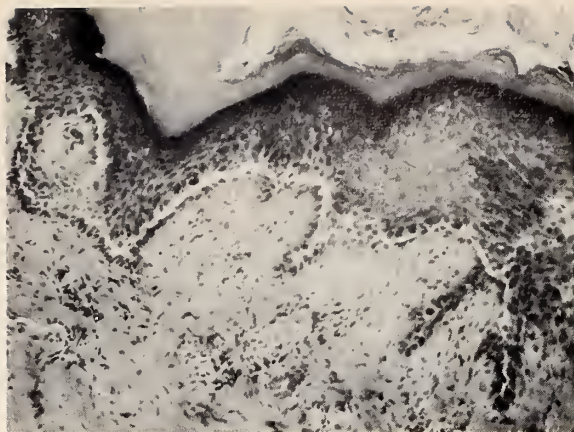


Figure 1.—Intraepidermal separation shown in a histological section of an early bullous lesion from a patient with pemphigus vulgaris.

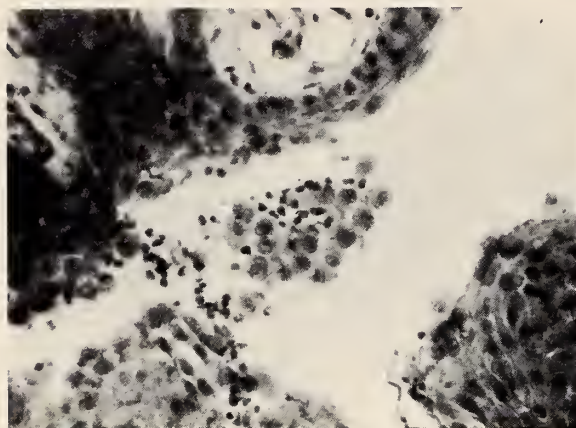


Figure 2.—High power view of Figure 1, demonstrating free floating, spherical, hyperchromatic epidermal cells in bullae termed acantholysis.

to heal when they rupture so that large denuded areas frequently become the outstanding clinical feature of the disease (Figures 3 and 4). The Nikolsky sign (the detachment of the horny layer for a long distance even on seemingly healthy skin produced by pulling the ruptured wall of a blister) is characteristically positive. The mucous membranes are the initial site of involvement in approximately 50 percent of the patients, a fact that has intrigued those who believe there is a strong possibility that pemphigus is caused by infection. Pemphigus vulgaris develops most frequently in persons between 40 and 60 years of age. It is rare in children and adolescents. The incidence is reported to be high in persons of Jewish extraction. Spontaneous remissions are rare and if the disease is not treated death invariably occurs, in an average



Figure 3.—Pemphigus vulgaris presenting usual clinical features of crusted, ruptured vesicles and bullae.



Figure 4.—Pemphigus vulgaris with unruptured flaccid bullae on noninflamed base.

of 14 months. With the advent of immunofluorescent techniques, it was hoped that less severe or self-limited forms of the disease might be





Figure 5.—Large verrucous, hypertrophic vegetations in the groin of patient with pemphigus vegetans.

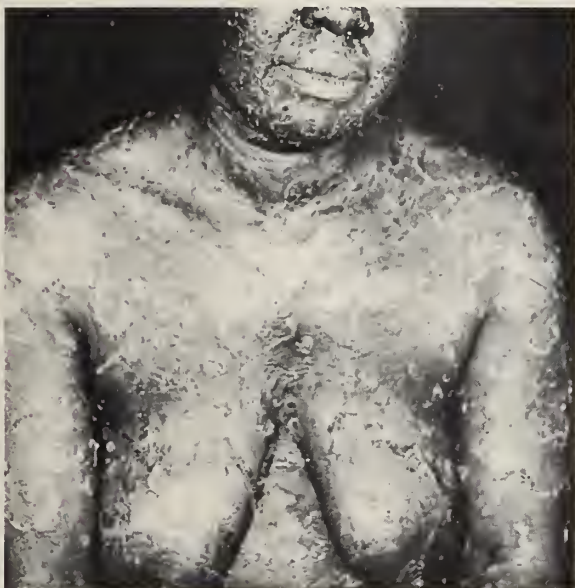


Figure 6.—Widespread exfoliative process in pemphigus foliaceus.

identified if they were masquerading as clinically unrecognized variants, but they have not been detected to date.

The primary lesion in pemphigus vegetans is a pustule and not a bulla. Large verrucous, hypertrophic vegetations studded with pustules form the clinical picture (Figure 5). The course is chronic and more benign than that of pemphigus vulgaris, with spontaneous remissions which may last for months and years. In a few cases lesions heal permanently. Pemphigus vegetans is, however, considered a variant of pemphigus vulgaris, into which it generally evolves.

In pemphigus foliaceus the bullae character-

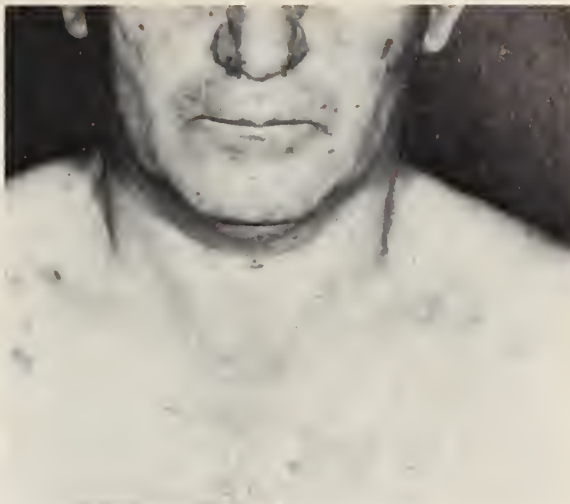


Figure 7.—Pemphigus erythematosus with sealy, hyperkeratotic, crusted lesions in the nose and malar regions.

istically occur high in the epidermis and rupture early, leaving shallow erosions. Intact bullae are rare and the patient usually has widespread erythema, scaling, oozing and crusting erosions (Figure 6) when first seen. The lesions frequently develop first on the face, and then slowly involve the entire body. Oral lesions are absent. The course is chronic and may last for years. In patients more than 50 years of age the disease is usually fatal but under 50 years it may subside in two to 20 years. Pemphigus foliaceus may occur in children. Brazilian pemphigus foliaceus (fogo selvagem) which is thought to be caused by a virus occurs with a high frequency in well circumscribed endemic foci in Brazil and to a lesser extent in the adjoining areas of Bolivia, Paraguay and Argentina.

Pemphigus erythematosus (Senear-Usher syndrome) is characterized by erythematous, sealy, hyperkeratotic, crusted lesions frequently developing in a butterfly pattern over the nose and malar regions (Figure 7). It may remain limited and benign or progress into pemphigus foliaceus. Although it has been considered a variant of the foliaceus form, immunofluorescent studies have shown patterns of fluorescence suggesting that it is related to lupus erythematosus.

### Immunofluorescent Studies

Beutner and Jordon,<sup>1</sup> using the indirect immunofluorescent (IF) technique, originally found antibodies directed against the intercellular sub-



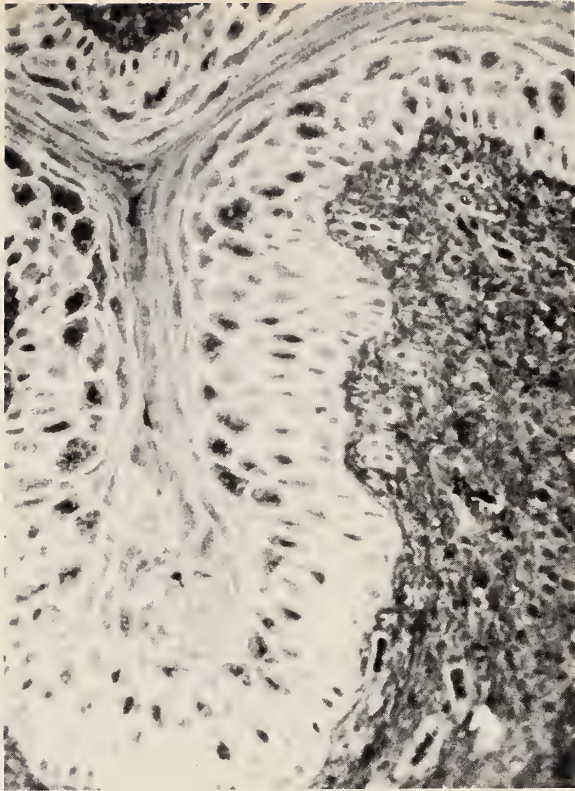


Figure 8.—Indirect immunofluorescent test, using monkey esophagus and serum from a patient with pemphigus vulgaris, demonstrates intercellular fluorescent pattern.

stance of stratified squamous epithelium in the serum of only eight of 13 patients with pemphigus vulgaris. Subsequent studies by them<sup>4,5</sup> and others<sup>6,7</sup> have revealed these antibodies in the serum of almost all patients with severe active pemphigus. The antibodies appear to be directed against a substance on the surface or rim of, or between epithelial cells especially of the stratum spinosum or prickly cell layer of the epidermis (Figure 8). These antigenic materials are present not only in epidermal tissues of autologous origin but also in similar tissues of homologous and heterologous species. They are also present in the epithelial tissue of the nasal and oral mucosa, gingiva, tongue, soft palate, uvula, anus, vagina, cornea, esophagus and rectum.<sup>4</sup> In the indirect IF technique, stratified squamous epithelium from humans, monkeys, rabbits or guinea pigs has been used as the substrate and appear<sup>5</sup> to give equally good results,<sup>4,8</sup> with some exceptions.<sup>4</sup> Epithelial stromal cle-

ments and parenchymal cells of over 30 other kinds of tissue have failed to yield positive reactions.<sup>4</sup>

An association was noted early between the severity of the disease process and the titer of intercellular antibodies.<sup>4</sup> Patients without lesions had no such detectable antibodies in the serum, whereas patients with extensive lesions had titers of 1:160 and even as high as 1:5120.<sup>5</sup> Serial determinations of antibody performed with patients with active pemphigus vulgaris during treatment with corticosteroids revealed lowering of antibody titers, with titers becoming negative immediately before or at about the same time that clinical manifestations of the disease disappeared. In one patient a recurrence of a positive titer or rising titers was followed by clinical relapse. This correlation between titers of intercellular antibodies and clinical severity of pemphigus was early proposed as a valuable prognostic aid and also a guide to the management of patients with pemphigus vulgaris treated with corticosteroids.<sup>7</sup> Some clinicians familiar with the pattern of fluctuations of these antibodies used it as an aid in the adjustment of dosages of corticosteroids.<sup>5,10</sup> Additional experiences, however, modified this view so that at present we<sup>11</sup> and others<sup>12,13</sup> are not convinced that therapy can be regulated by following serial serological titers, and the clinical response to therapy remains the most valuable criterion for determining the dosage schedules.

In an effort to further understand the nature of antibodies in pemphigus, serum immunoglobulins have been examined. Using a quantitative technique in the study of 13 patients with pemphigus vulgaris, Lim and Fusaro<sup>14</sup> found IgG and IgM to be depressed, and IgA to be elevated. Waldorf and Rogentine<sup>15</sup> studied specimens from 21 patients with pemphigus with the agar gel diffusion technique and found that the mean values of IgA, IgM, IgG and IgD were all below normal. Grob and Inderbitzin<sup>16</sup> examined immunoelectrophoretic patterns of the serum in 15 patients with pemphigus and found the mean concentrations of IgA elevated, IgM decreased and IgG normal. Neither the activity of the disease nor the titer of intercellular antibodies could be correlated with the level of IgG or IgA in the serum. The intercellular antibodies appear to be essentially in the IgG fraction and



studies with specific antisera to human IgA and IgM have yielded either completely negative, weak or doubtful reactions.<sup>5</sup>

Using the direct IF technique on biopsy specimens obtained from involved skin of patients with pemphigus vulgaris, antibodies have been demonstrated in combination with antigens in the areas of the intercellular substance and on the surface of acantholytic cells of the prickle cell layer of the epidermis composing the wall of the bullae.<sup>4</sup> Binding of IgG in this same intercellular pattern has also been detected in biopsy of "normal" skin from patients with pemphigus vulgaris. The uninvolved skin from three patients with pemphigus vulgaris controlled by corticosteroids was studied<sup>6</sup> by the direct application of fluorescein conjugated rabbit antihuman gamma globulin and no binding of gamma globulin could be observed. One of these three patients was also studied at a time when the disease was active and gamma globulin was found in the uninvolved skin in the pemphigus vulgaris pattern. In four patients with pemphigus vulgaris, the presence of complement and globulin concomitantly bound to the intercellular substance of the prickle cell layer of the epidermis in biopsy sections of the skin adjacent to the bullous lesions was demonstrated by the direct IF technique, suggesting that the presence of gamma globulin is part of an antibody-antigen reaction.<sup>17</sup>

The exact role of these antibodies in the pathogenesis of pemphigus is still undetermined.<sup>6</sup> It has been postulated that these antibodies are elicited by tissue constituents which have been altered as a consequence of disease and thereby rendered antigenic. They may also conceivably have some primary causal role or participate secondarily to produce additional tissue damage. Beutner et al<sup>18</sup> have marshalled an increasing body of circumstantial evidence which supports the view that the intercellular antibodies may play a pathogenic role in the disease. Antibodies to intercellular areas of stratified squamous epithelium are postulated to be auto-antibodies as they: (1) combine with their homologous antigen *in vivo*; (2) combine at the site of primary histopathologic changes observed with the light microscope; (3) appear to fix complement *in vivo*; (4) have been found only in patients with pemphigus thus far; (5) occur in virtually all cases

of active pemphigus; (6) fluctuate in titer with severity of disease process; and (7) in at least one case were demonstrated before lesions developed. On the basis of these observations an underlying immunoglobulin abnormality has been considered to be responsible for formation of intercellular antibodies and development of the disease process in some patients with pemphigus.

In one study,<sup>4</sup> monkeys were injected intradermally at multiple sites with 0.1 ml of serum from patients with pemphigus which contained antibodies to intercellular substance. Optimal binding of gamma globulin occurred in approximately 24 hours and binding to the intercellular substance between the epidermal cells occurred at or near the site of injection predominantly in the region of the basal layer. That acantholysis did not develop would seem to be evidence against direct involvement of the antibodies in production of lesions of pemphigus.<sup>7</sup> This evidence is supported by the fact that gamma globulin can be demonstrated fixed to the intercellular areas of the epidermis in apparently normal skin of patients with pemphigus. Antibodies fixed *in vivo* to their antigen in the skin cannot, however, justifiably be assumed to be completely devoid of pathological significance.<sup>7</sup> We are in agreement with Beutner<sup>19</sup> that further study is required to determine whether the observed immune responses in pemphigus are etiologically related to it or are a consequence of the skin changes.

Grob and Inderbitzin<sup>20</sup> have experimentally produced antiepithelial auto-antibodies by immunizing rabbits with a fraction from the epithelium of rabbit esophagus. On indirect IF testing antiepithelial antibodies of two of six rabbits were bound to the basal cells only, clearly outlining their borders. The antiepithelial antibodies present in the serum of the four other rabbits were bound *in vitro* to the entire squamous epithelium of the rabbit esophagus, producing a picture indistinguishable from that obtained with serum of patients with pemphigus. The skin and the esophagus of the six successfully immunized rabbits were found to be free of *in vivo* bound antiepithelial antibodies, suggesting the existence of an efficient barrier between the epidermis and the plasma. In a later study<sup>21</sup> intraepidermal clefts based on acantholysis were produced in rabbits with high titers of antiepithelial auto-antibodies. The thin epidermis of the immunized animals and



of control animals was first made moderately acanthotic by repeated epicutaneous applications of a solution of sodium lauryl sulfonate. The acanthotic skin was then exposed to dry ice to initiate a vascular leakage of plasma into subepidermal tissue. The epicutaneous application of both sodium lauryl sulfonate and dry ice, it was postulated, altered the permeability of the dermal-epidermal junction sufficiently to allow passage of plasma into the epidermis. The investigators concluded that their findings support the view that acantholysis in pemphigus is an immunologic phenomenon.

Albin and Beutner<sup>22</sup> prepared aqueous and ethanol extracts of esophageal epithelium. Immunization of rabbits with an ethanol-soluble extract of bovine esophageal mucosa incorporated in Freund's adjuvant elicited an antibody response as judged by the criterion of indirect IF staining of intercellular areas of stratified squamous epithelium.<sup>23</sup> No conclusive evidence for the *in vivo* binding of IgG was observed in biopsy or autopsy tissues. Irregularly shaped "bullous-like" cutaneous lesions approximately 2 to 3 cm in diameter appeared in inoculated areas of rabbit epidermis. The animals having bullous-like lesions had pemphigus-like auto-antibodies with indirect IF titers ranging from 1:16 to 1:64. Histologic studies of rabbit epidermal lesions disclosed, however, the presence of what appeared to be subepidermal-like bullae.<sup>24</sup>

The indirect IF technique appears to be quite as reliable diagnostically as histopathology<sup>5</sup> but certainly does not replace it. The test may be positive in some active cases of the four types of pemphigus but this test cannot be used to distinguish them. Titers observed in serum obtained from patients with Brazilian pemphigus foliaceus were found to be higher than those of any of the other forms of pemphigus, and this has been suggested to be a characteristic of the disease.<sup>25</sup> A further speculation is that there are slight differences in pathogenic mechanisms between the different varieties of pemphigus. Some arthropod-borne infectious agent endemic in the fogo selvagem foci in South America may share antigenic determinants with intercellular substances of stratified squamous epithelium.<sup>5</sup>

The exact value of the indirect IF test in the diagnosis of pemphigus, where lesions may be few or non-diagnostic clinically, is undetermined.

In some instances it is positive and of great aid in establishing diagnosis early, and in others it has been negative. In one patient intercellular antibodies characteristic of pemphigus were demonstrable in the serum for years before clinical and histologic evidence of pemphigus vulgaris developed, and a potential form of pemphigus vulgaris was postulated to exist.<sup>10</sup> We have examined the serum of close relatives of patients with pemphigus but have been unable to detect such antibodies.

In almost all patients with well-documented active pemphigus the serum has demonstrable titers of pemphigus antibodies but some exceptions have been encountered. These disturbing discrepancies have been attributed to several factors other than errors in technique.<sup>9</sup> Some have been attributed to the prozone phenomenon, or failure to demonstrate intercellular antibodies at low dilutions of the patient's serum. This was thought to be due to the interference of antinuclear antibodies as artificial mixtures of specimens of serum containing only intercellular antibodies with other specimens containing antinuclear antibodies were found to yield prozones.<sup>18</sup> None of the fogo selvagem serum included in one study<sup>25</sup> contained antinuclear antibodies, yet essentially all fresh serum from patients with pemphigus of this type gave prozones. Patients with pemphigus also may have high titers of antinuclear antibodies in the serum and a prozone may not be encountered.<sup>10</sup> Prozones can also be produced by mixing fresh normal human serum with serum containing high titers of pemphigus antibodies.<sup>9</sup>

Somewhat comparable inhibition of the indirect IF reaction has been produced by mixing a serum containing rheumatoid factor with an active pemphigus serum. Most pemphigus serum that has been tested appears to contain some rheumatoid factor suggesting<sup>18,26</sup> that this factor may be the inhibitor responsible for the prozone. Other mechanisms which have been postulated<sup>9</sup> include presence of intercellular antigens in the serum, leading to formation of antigen-antibody complexes, presence of blocking antibodies, and enzymatic degradation of labile intercellular antigens either by enzymes in fresh serum or by serum activation of enzymes present in cryostat cut substrate sections. Prozones may result from interference due to presence of multiple tissue antibodies resulting in consumption of labelled antiglobulin by one of the tissue reactive anti-

bodies to exclusion of others. The test, however, has been demonstrated to be highly reproducible among laboratories using identical techniques.<sup>25</sup> Variable titers, ranging from completely negative reactions to a titer of 1:160, were reported in replicate experiments on blood drawn all at one time from one subject and on specimens drawn serially from one subject.<sup>9,25</sup> This variation has been ascribed to an inhibitor.

The optimal substrate for use in the indirect IF test has not been determined. This is a matter of some importance since a broad spectrum of specificities of pemphigus antibodies has been observed in selected specimens from patients with the disease. Antiserum contains antibodies reactive with different antigenic determinants in the intercellular substance of various stratified squamous epithelia, and some differences will also occur between epithelial tissues used for substrates obtained from individual rabbits, monkeys and humans.<sup>9</sup>

**D**irect IF staining of cytoplasm of epidermal cells and particularly acantholytic cells has been observed in biopsy sections and Tzanck preparations of bullae from six patients with pemphigus vulgaris.<sup>27</sup> Inderbitzin and Grob<sup>21</sup> immunized 11 rabbits, using a preparation of a fraction from epithelium of a rabbit esophagus which reacted with antiepithelial antibodies of pemphigus. The antibodies which developed in the serum of one rabbit became bound to the cytoplasm of cells of esophageal epithelium while neither the cell nucleus nor the cell border bound the antibodies. Cytoplasmic IF staining<sup>19</sup> has also been demonstrated, using human skin but not guinea pig lip as substrate, with serum from patients with a variety of diseases including rheumatoid arthritis, hypersensitivities, urticaria and eczema. Cytoplasmic antibodies deserve additional study but do not appear to be associated with any specific skin disease.

Indirect IF staining patterns identical to those observed with the serum of patients with pemphigus have been encountered in other conditions. In 1960 Szulman, using indirect IF for visualization, studied the histological distribution of blood group substances A and B in tissues from man.<sup>28</sup> The immunofluorescent pattern with stratified epithelia seemed to be identical with that obtained using serum from patients with pem-

phigus. Grob and Inderbitzin<sup>29</sup> absorbed blood group antibodies from the serum of patients with pemphigus before doing the indirect IF test and found that the absorption did not interfere with antiepithelial activity, indicating non-identity of blood group antibodies with pemphigus antibody. Human blood group serum did, however, produce an intercellular pattern; but the concentration of anti-A and anti-B immune globulins in human serum were considered never to reach the threshold level necessary for induction of a positive IF test. A pattern of immunofluorescence similar to that of pemphigus using indirect IF has also been encountered with the antilymph node serum<sup>30</sup> and serum from some patients with severe burns.<sup>31</sup>

The intercellular pattern of fluorescence was demonstrated as a falsely positive reaction in 24 of 75 patients with diseases other than pemphigus by Anderson et al.<sup>11</sup> A relationship was found between the presence of anti-B isohemagglutinins and intercellular fluorescence as demonstrated by indirect IF, using the esophagus of a fetal rhesus monkey (*Macaca mulatta*) as the substrate. When the anti-B isohemagglutinin titer was reduced or abolished, after absorption with B substance, the intercellular pattern was abolished or reduced considerably. These investigators stressed the importance of the blood type of the substrate employed in the indirect IF technique and the blood type of the patient, so that this factor which may give rise to error in interpretation of intercellular fluorescence is excluded.

## Electron Microscopic Studies

Wilgram et al<sup>32</sup> concluded that the primary event which leads to acantholysis was damage to the tonofilaments. Braun-Falco and Vogell<sup>33,34</sup> initially considered the desmosome to be the chief site of involvement. Braun-Falco<sup>35</sup> concluded that dissolution of existing intercellular bridges in pemphigus vulgaris did not occur but that the epidermal cells were unable to form normal desmosomal contacts and the number of desmosomes was thereby diminished. Hashimoto and Lever<sup>36</sup> found that the first ultrastructural alteration consisted of damage of the intercellular substance, which is composed of amorphous material. The major portion, however, seems to be derived from the membrane-coating granules of Matoltsy and Parakkal. In pemphigus these membrane-coating



granules were not only increased in number but appeared abnormal because of their larger size and internal structure. Hashimoto and Lever<sup>36</sup> postulated that these abnormal granules are either providing cement which is defective in its adhesive capacity or are carrying some substances or enzymes which exert lytic effect on the intercellular cement. Further, they conjectured that these substances might be able to sensitize the patient to produce auto-antibodies. These granules might also carry lytic enzymes which play an important role in the physiological detachment of cells in upper layers of epidermis. Komura examined early cutaneous lesions in a patient with pemphigus foliaceus.<sup>37</sup> The first morphological alteration during acantholysis in pemphigus foliaceus seemed to be dissolution of desmosomes, especially its cementing substance, and frequently the tonofilaments detached from attachment plates of their corresponding desmosome. He concluded that the mode of acantholytic bullae formation in pemphigus foliaceus was somewhat different from that seen in pemphigus vulgaris.

Grace<sup>38</sup> recently described mycoplasma-like pleomorphic forms in those sites in cells and intercellular spaces of the rete malpighii where antibodies have been demonstrated. The tentative conclusion was that the forms constitute the antigen evoking the antibodies and also produce the clinical and pathological manifestations of pemphigus vulgaris and pemphigus vegetans.

### Associated Immunological Diseases

Circumstantial evidence suggests that pemphigus vulgaris may be a part of a spectrum of disorders intimately but not necessarily causally associated with other immunological disorders. Pemphigus has been observed to be associated with such disorders in a greater frequency than by chance.<sup>6</sup> Pemphigus has been reported in the same patient with systemic lupus erythematosus and thymoma,<sup>6,39</sup> myasthenia gravis,<sup>5</sup> thymoma and myasthenia gravis,<sup>40</sup> rheumatoid arthritis,<sup>41</sup> and lupus erythematosus.<sup>41,42</sup>

The immunological changes characteristic of both pemphigus and lupus erythematosus have been demonstrated in patients with the Senear-Usher syndrome, suggesting that this syndrome results from a combination of pemphigus and lupus erythematosus.<sup>41,42</sup> Circulating and fixed intercellular immunofluorescent staining diagnostic of pemphigus and fixed *in vivo* immuno-



Figure 9.—Bullous pemphigoid. Tense bullae superimposed on erythematous, edematous plaques.

globulin and complement at the dermal-epidermal junction of skin lesions characteristic of lupus erythematosus have been observed.

### Bullous Pemphigoid

Bullous pemphigoid, a bullous disease frequently confused with pemphigus, was clearly distinguished in 1953 by Lever,<sup>2,3,43</sup> who based his distinction on Civatte's<sup>44</sup> histological studies described a decade earlier. The bullae of this disease are tense, may reach considerable size, are irregular in outline, and show a good tendency to heal following rupture (Figure 9). The bullae are subepidermal in location and acantholytic

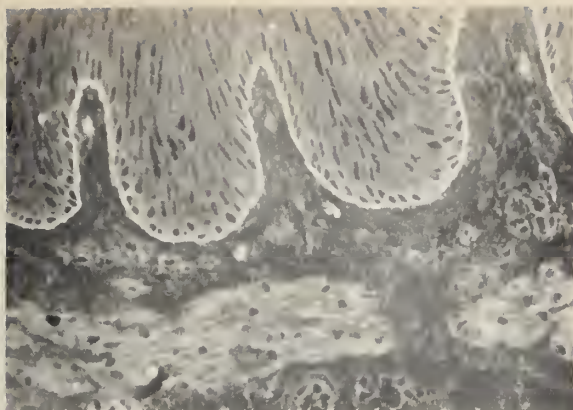


Figure 10.—Indirect immunofluorescent test, using monkey esophagus and serum from a patient with bullous pemphigoid, demonstrates fluorescence of basement zone of dermal-epidermal junction.

cells are absent. Erythematous, edematous, ser-piginous plaques, some with active borders, showing central healing are also present. The course is that of exacerbations and remissions over months and years. Without treatment the mortality rate among patients over 65 is approximately 57 percent. By indirect IF examinations, antibodies specific for the basement zone at the dermal-epidermal junction (Figure 10) may be demonstrated in 80 to 90 percent<sup>15</sup> of patients with severe and active disease. Titters have ranged from 1:20 to 1:2560.<sup>5</sup> Their absence from the serum of some patients suggests that the circulating antibodies might be bound *in vivo* and that in early stages of the disease they may not be present in demonstrable concentrations in serum. Antibodies would thus appear in serum only after available antigenic sites in the basement zone have been saturated by the auto-antibodies. Another possibility is that the absence in some of the cases with active lesions indicates that bullous pemphigoid is probably not a homogeneous syndrome.<sup>46</sup> The basement membrane antibody has been found to be IgG<sup>45</sup> and to fix complement.<sup>47</sup> A few specimens of bullous pemphigoid serum, however, have been found to contain IgM basement membrane zone antibodies.<sup>47</sup> The antibodies against the basement membrane zone of the epidermis have not been found to date in the serum of patients with other vesicular or bullous diseases and a positive result of IF studies makes possible differentiation of bullous pemphigoid from dermatitis herpetiformis. Only positive results are diagnostically decisive.<sup>5,46</sup> The basement membrane antibodies have also been found in

blister fluid of patients with bullous pemphigoid.<sup>47,48</sup> Immunofluorescent studies are of no aid in distinguishing bullous pemphigoid due to a drug eruption from that associated with cancer or from that in which no etiological factor is detectable.<sup>10</sup>

Direct IF staining of the basement membrane has been demonstrated in bullae and adjacent skin in patients with bullous pemphigoid. Similar direct IF staining of the basement zone has also been demonstrated in lesions of patients with discoid lupus erythematosus and in lesions and uninvolved skin of patients with systemic lupus erythematosus.<sup>15</sup> Most recently granular deposits of IgA in the basement membrane zone of uninvolved skin from ten of twelve patients with dermatitis herpetiformis have been described,<sup>49</sup> supporting earlier findings of Cornane.<sup>50</sup> The absence of such granular deposits in bullous and peribullous skin in the majority of patients with dermatitis herpetiformis has been explained as owing to phagocytosis of these complexes by numerous polymorphonuclear leucocytes present in the areas.

## Treatment

The use of corticosteroid therapy in management of pemphigus vulgaris has lowered the mortality rate of this previously invariably fatal disease to 30 to 40 percent.<sup>51,52</sup> The most frequently utilized dosage schedule<sup>3</sup> is 24 to 36 tablets (5mg) of prednisone per day to begin with. If new lesions appear during the next five days, the dosage is then increased by 12 tablets per day. This dosage is continued until full healing has occurred, usually in six to eight weeks, and then reduced to a maintenance level. Alternate day therapy for maintenance offers a possibility of reducing the side effects of long term steroid therapy.

The immunosuppressive agents are in the process of being evaluated because of the serious side effects of prolonged high doses of steroid therapy and the possibility that pemphigus may in part be autoimmune in nature. At the present level of experience Lever<sup>13,43,53</sup> considers methotrexate as the treatment of choice in localized pemphigus foliaceus and pemphigus erythematosus. Methotrexate is definitely contraindicated in pemphigus vulgaris if the disease is severe or rapidly advancing. Three groups of patients with pemphigus vulgaris are, however, considered candidates for methotrexate therapy. These are patients in



whom the disease is early and localized, those in remission after administration of high doses of prednisone, and those in whom prednisone is causing serious side reactions.

In the first group, therapy may be required for a period of two to four months before improvement is obtained. In the second group, with the disease barely suppressed by maintenance doses of prednisone, methotrexate should be given for two months before the dose of prednisone is lowered. The patient with severe disease who is being treated with massive doses of prednisone for the first time should be given 180 to 300 mg of prednisone a day for six to eight weeks to suppress the disease. Prednisone should be reduced, if possible, to a maintenance dose of 40 mg a day, and methotrexate in weekly doses can then be added. Prednisone is then gradually reduced until it can be discontinued, and subsequently the methotrexate dose is gradually reduced by about 5 mg a month if possible. In patients having serious side reactions to prednisone, the dose of that drug should be reduced to the lowest safe level, probably 40 mg a day, and methotrexate then added. Parenteral is preferable to oral administration in the beginning because larger doses can be tolerated without nausea.

An initial test dose of 25 mg methotrexate can be given, intramuscular injections at weekly intervals in doses of 50 mg or possibly less if smaller doses suffice to suppress clinical manifestations. In some instances where pemphigus was diagnosed very early, with lesions limited to mucous membranes of the oral cavity or anogenital area, or the disease has an apparently mild course, methotrexate has been satisfactorily used without preceding corticosteroid therapy. In a number of other patients, methotrexate therapy combined with continued low doses of corticosteroids (in the range of 15 to 20 mg a day of prednisone) were necessary. The therapeutic doses of corticosteroids and methotrexate must be fitted to the needs of each patient. Although the exact status of this therapeutic agent has not been established, methotrexate has greatly improved the outlook for some patients with pemphigus<sup>53</sup> by reducing the hazards of continued corticosteroid therapy.<sup>54</sup>

Wolff and Schreiner<sup>55</sup> gave azathioprine to four patients receiving corticosteroids and found it beneficial. A considerable latency period, however, may precede clinical improvement, and

lasting remissions require continuous and long term therapy. Azathioprine treatment alone was ineffective and its advantage was considered to reside in its "steroid saving" effect, with avoidance of the serious side effects and late sequelae of steroid therapy. Burton, et al.,<sup>56</sup> treated four patients with pemphigus vulgaris who were being maintained by systemic administration of corticosteroids. Three were enabled to discontinue steroid therapy, the fourth could not tolerate the drug. In two patients relapse occurred when therapy was stopped but was again controlled when azathioprine was resumed.

Ebringer and Mackay<sup>57</sup> treated one patient with pemphigus vulgaris with cyclophosphamide in doses up to 200 mg daily in four separate courses over a three-year period. This allowed for a gradual reduction in high maintenance doses of prednisone, and remissions were induced. McKelvey<sup>58</sup> gave cyclophosphamide to a patient whose pemphigus was resistant to systemic steroid therapy and who had severe steroid reaction, including diabetes mellitus, osteoporosis and compression fractures of the lumbar spine, peripheral edema and profound steroid myopathy. At first 200 mg of cyclophosphamide a day was given by mouth, and this was gradually reduced to 100 mg a day over a four-month period. With this schedule prednisone could be reduced to 10 mg every other day from the usual standard maintenance dose. We have treated two patients with similar favorable results. Lever<sup>53</sup> believes that methotrexate represents the treatment of choice for patients with pemphigoid and we have successfully treated one such patient with cyclophosphamide.

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# Q Fever in Los Angeles County

## Serological Survey of Human and Bovine Populations

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● *Q fever is endemic and enzootic in Los Angeles County. A serological survey conducted in 1949 is compared with a current survey. Infection in dairy herds is now almost universal, while the prevalence of positive complement fixation titers in man only increased from 1.2 percent to 2.3 percent ( $p < 0.10$ ). The relative stability in man is accounted for by the increase in temperature requirements for milk pasteurization, the decrease in consumption of raw milk and the decrease in the number of dairy farm foci.*

Q FEVER WAS FIRST RECOGNIZED in Los Angeles County in 1947, when an outbreak of the disease was described by Young.<sup>1</sup> Shortly thereafter, extensive epidemiologic studies<sup>2,3</sup> indicated that Q fever was enzootic among dairy cattle in Los Angeles County and that the prevalence of Q fever complement fixation (CF) antibodies in the human population was 1.3 percent.

Since the initial studies were completed in 1948-1949, the proportion of cattle with serologic evidence of infection has increased from more

than 10 percent<sup>4</sup> to 62 percent in 1960.<sup>5</sup> As numerous residential areas have since been constructed around previously isolated dairy farms, it seemed likely that the prevalence of Q fever CF antibodies in the general population would have increased in the 20-year period following 1948.

In 1966, five cases of Q fever were reported from a particular geographical area of Los Angeles County.<sup>6</sup> All the patients lived or worked near dairy farms from which the herd milk samples had detectable Q fever antibodies indicative of infection with *Coxiella burnetii*. None of the five patients had a history of occupational exposure to infected livestock or of raw milk ingestion. To determine if this outbreak was a reflection of an increased incidence of subclinical Q fever infection, a serological survey was undertaken to determine the prevalence of Q fever CF antibodies in the human population. In addition, milk samples from all dairy herds in Los Angeles County were tested for the presence of Q fever capillary agglutinating antibodies. This paper presents the findings of these two surveys.

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## Methods and Materials

*Study area.* Los Angeles County encompasses 4,083 square miles. There were 7,057,720 people living in the county in 1967.<sup>7</sup> The climate is semiarid with few temperature extremes throughout the year. There are 268 dairy farms, many of them situated in the midst of suburban residential communities.

The County of Los Angeles Health Department has jurisdiction over the entire county, with the exception of the cities of Long Beach, Pasadena, and Vernon. These three cities have a combined population of approximately 500,000. The area of jurisdiction is divided into 23 separate health districts. Q fever has been a reportable disease since 1955.

*Survey of human population.* All individuals seen in the venereal disease clinics of the County Health Department (including old and new cases and contacts) during March, 1967, constituted the study population. A standard questionnaire was completed by each participant. Information was obtained regarding past or present farm employment, farm animal contact, raw-milk ingestion, and history of pneumonia. The respondent also indicated his length of residence at his present address, as well as his total period of residence in Los Angeles County.

*Serological procedure.* A portion of the serum taken for the routine Venereal Disease Research Laboratory (VDRL) test was titrated for the presence of Q fever antibodies by the relatively insensitive complement fixation (CF) test. A commercial antigen\* prepared from the American Nine-Mile strain was used for the complement fixation test. Nonspecific reactions in blood from patients with syphilis are not significant problems with the purified antigen now used.<sup>8</sup> In addition to controlling for nonspecific reactions as provided by the standard test procedure described by the manufacturer,<sup>3</sup> a Rickettsialpox antigen was used as a test control. An adaptation of the microtiter procedure described by Sever was employed.<sup>9</sup> A reaction was considered positive and indicative of past infection with *Coxiella burnetii* when definite, 3 to 4 plus (75 to 100 percent) complement fixation occurred at the starting dilution of 1:8 or at a greater dilution.<sup>10</sup> The presence of CF antibodies in these

specimens was confirmed by the Viral and Rickettsial Disease Laboratory of the California State Department of Health.

*Survey of dairy herds.* All herds of dairy cattle in Los Angeles County were sampled during the months of April, May, and June 1967. A single pooled sample of milk from all dairy cattle within a given herd was tested for the presence of Q fever antibodies by the capillary agglutination (CA) test.<sup>11</sup>

## Results

*Description of the study group.* Serum samples were obtained from 394 individuals attending the venereal disease clinics during the month of March 1967. The age range for the group was five to 77 years; more than three-quarters of the persons in the group were between 17 and 31 years old. Fifty-nine percent of those sampled were males, and 41 percent were females.

*Geographical distribution.* The study group represented 274 of the 1,207 census tracts in the county. Participants came from widely separated parts of the county. As a result, persons from all 23 health districts were included in the survey and the maximum number in any given census tract was five. More than 80 percent of the group had lived at their stated address for five years or less and in Los Angeles County for 22 years or less.

*Positive Q fever complement fixation titers.* Nine of the 394 specimens of blood (2.3 percent) had detectable Q fever CF antibodies; seven had titers of 1:8, and two had titers of 1:16 (Table 1). The VDRL screening test was reactive in two of the nine positive specimens (Cases 114 and 311).

*Epidemiologic attributes associated with positive Q fever CF antibody titers (Table 1).* Persons with positive Q fever CF antibody titers were older than those with negative titers; the median ages were 37 and 25 years, respectively. Most positive Q fever CF antibody titers were detected in females (67 percent), while there were more males in the larger group with negative titers. The significance of this observed difference in sex distribution is unknown. Duration of residence at the stated address or at any address in Los Angeles County was slightly less in those with positive titers.

Of the nine persons with positive CF titers, eight gave a positive response to at least one of the questions regarding farm employment, livestock

\*Prepared by Lederle Laboratories, Pearl River, N.Y.



TABLE 1.—*Characteristics of individuals with detectable Q Fever antibodies in the blood\**

Case	Age	Sex	CF antibody titer†	Years at residence	Years in Los Angeles County	Farm Employment	Contact with:			Drank raw milk	Distance in miles of current residence from dairy farm
							Cattle	Sheep	Goats		
37	5	F	8	3	4	—	—	—	—	—	> 1.0
54	37	F	8	4	4	+	+	+	+	+	0.4
111	19	F	16	< 1	19	—	—	—	—	+§	0.2
114	50	F	8	< 1	15	—	+	+	+	+	> 1.0
139	46	F	8	1	7	+	—	—	—	—	0.3
211	35	F	8	1	20	—	+	—	—	+§	> 1.0
228	19	M	8	< 1	< 1	+	+	—	—	—	> 1.0
311	49	M	8	< 1	25	+	+	+	+	+§	0.2
352	43	M	16	3	22	+	+	—	—	+§	> 1.0

\* Serum obtained from 394 Venereal Disease Clinic patients in Los Angeles County, March, 1967.

† Reciprocal of serum dilution.

§ While residing in Los Angeles County.

contact, or raw-milk ingestion. Five of the nine had been engaged in farm employment, and six had had contact with cattle. Three of the six with exposure to cattle were also exposed to sheep and goats, any of which may harbor *Coxiella burnetii*. All but three had ingested raw milk. One of these three had no history of farm employment or contact with cattle, sheep, or goats. In the group of 385 persons with CF negative blood, only a small percentage had worked on farms (20 percent), had been exposed to livestock (17 percent to cattle, 6 percent to sheep, 7 percent to goats), or had ingested raw milk (20 percent).

The significance of proximity of previous residence to an infected dairy was not adequately investigated. All that can be stated is that five of the nine previously infected persons currently lived at an address located too far from an infected dairy to be of any epidemiologic significance.<sup>3</sup>

*Herd samples from dairy cattle.* Composite milk samples were obtained from all of the 268 dairy herds in Los Angeles County during April, May, and June 1967. Two hundred sixty-six or 99 percent of these pooled herd samples were positive for Q fever antibodies by the CA test. One negative herd was at an agricultural college, and the other negative sample was from a commercial herd in the northern part of the county.

## Discussion

Since the initial discovery of Q fever in Los Angeles County, numerous reports on the presence of *Coxiella burnetii* antibodies in local dairy cattle have appeared in the literature.<sup>5</sup> Serological evidence for infection has been found in dairy

herds from 35 states, indicating its current widespread prevalence. The most recent published study on the enzootic prevalence in southern California (mostly Los Angeles County) appeared in 1960 and pointed out that the infection in dairy herds was almost universal (98 percent).<sup>5</sup> In addition, the percentage of cows with detectable Q fever antibodies noted within some infected herds was 62 percent, whereas in 1949 approximately 10 percent had detectable CA antibodies.

This remarkable increase in the prevalence of Q fever antibodies among dairy cattle in Los Angeles County, coupled with the occurrence of a small outbreak of the disease in the human population in a specific area of the county,<sup>6</sup> prompted the County of Los Angeles Health Department to re-examine the prevalence of detectable Q fever CF antibodies in county residents. Further, because of the increasing number of homes built adjacent to dairies, an increase in Q fever infections had been expected.

This expectation was especially pertinent, since airborne spread of *Coxiella burnetii* from infected dairy farms to nearby residences had been thought to be one of the chief modes of spread of Q fever.<sup>12</sup>

The survey discussed in this paper revealed that the current prevalence for previous evidence of Q fever infections was 2.3 percent compared with 1.2 percent in 1949. The rates are not significantly different in the two groups ( $p < 0.10$ ). The current group was composed of individuals who attended the venereal disease clinics for a complaint of illness or for a premarital serological test for syphilis (STS); the group sampled in 1949<sup>4</sup> was composed of persons obtaining a routine pre-

marital sts. Although the groups were not chosen in an identical manner, both groups represented diverse geographical areas and were not selected for occupation or for distance of residence from a dairy. The type of serological test employed in this study was similar to that used in the 1949<sup>1</sup> investigation, and the criteria for previous evidence of Q fever infections were the same in both studies.

Consequently, during the past 20 years the prevalence of Q fever in the adult human population probably had not increased significantly, despite the almost universal appearance of bovine infection.

The relative stability of the prevalence of Q fever in Los Angeles was unexpected. Factors were sought which would account for this stable prevalence. Following the increase in the temperature requirements for milk pasteurization, pasteurized milk no longer was contaminated with *Coxiella burnetii*.<sup>13</sup> Raw-milk consumption over the past two decades has fallen from 20,196 gallons per day to 4,411 gallons per day, while the population has doubled in the same time.<sup>14</sup> Although residential areas have grown rapidly around dairy farms and herd infection with *Coxiella burnetii* is now almost universal in the county, the number of dairy farm foci has decreased considerably. In 1949, there were 595 individual

dairy farms. By 1967, the number had fallen to 268, and many of these had moved to a central area in the county. These several factors may account for the stability of the prevalence of Q fever CF antibodies in the population of Los Angeles County over the past 20 years—provided our sample is truly representative.

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## LESS THAN THROMBECTOMY

"Thrombectomy for the garden-variety of venous thrombosis is not routinely desirable. I think that interruption of the cava or superficial femoral—I prefer the cava — is preferable. An accomplished vascular surgeon can get by with thrombectomy, but I know of three patients who died because thrombectomy was done by surgeons who were not capable of doing a vascular operation. These patients would have lived if the surgeons had simply put a ligature in or put a clip on. I think that there has been too much emphasis on thrombectomy."

—ALTON OCHSNER, M.D., New Orleans

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# Specialty Conferences

## Myotonia

### A Review of Its Clinical Implications

Discussions by GAURANG P. BHATT, M.D., NAZHIYATH VIJAYAN, M.D.,  
PIERRE M. DREYFUS, M.D.

*Neurologic Grand Rounds held at the Sacramento Medical Center,  
University of California, Davis, School of Medicine.*

DR. DREYFUS: THE SYMPTOMS AND SIGNS of muscle disease, particularly when they are mild or evanescent, can easily be misinterpreted, with inappropriate medical treatment resulting.

Myotonia, when elicited, is frequently and erroneously considered symptomatic of irreversible muscle damage, when in fact it may be a sign of a benign or treatable condition. It seems therefore appropriate to review the clinical significance, pathophysiologic factors and therapy of this condition.

Myotonia can be defined as a state of increased muscle tone which results from active contraction and which perseverates for an unusually long time. The patient complains of exaggerated spasm or "cramp" of a group of muscles and the subsequent inability to relax these muscles. Whereas cold, excitement and vigorous exercise tend to aggravate myotonia, repetitive contractions may enhance relaxation and decrease the spasm.

On clinical examination, myotonia can be elicited by instructing the patient to grip the examiner's hand forcefully and then to let go as promptly as possible (hand grasp test). In the presence of myotonia percussion of the thenar eminence

brings about opposition of the thumb, and relaxation of muscle contraction is slow. Percussion of the tongue against a tongue depressor causes a persistent dimpling of the surface (percussion myotonia). This phenomenon should be distinguished from myoedema, a local bulge induced by tapping a muscle of a cachectic patient. Whereas the muscles of patients afflicted with myotonia may appear to be large, their strength tends to be reduced. Electrical stimulation of the muscles brings about an exaggerated response followed by slow relaxation. Figure 1 compares the electromyographic responses recorded in other pathological states with the response found in myotonia. When the response is electronically translated into noise, it sounds like a "dive bomber."

Dr. Bhatt will now present a case in which myotonia constituted the main symptom.

*Dr. Bhatt:* A 16-year-old high school boy was admitted to the hospital with the chief complaint of muscle stiffness. At the age of eight the patient first noticed that he had trouble starting to run. After running a short distance his muscles would stiffen and start to ache, but if he persisted in his efforts the ache and stiffness would disappear. Even at rest his muscles often felt "tight." Occasionally when he tried to run the muscle stiffness

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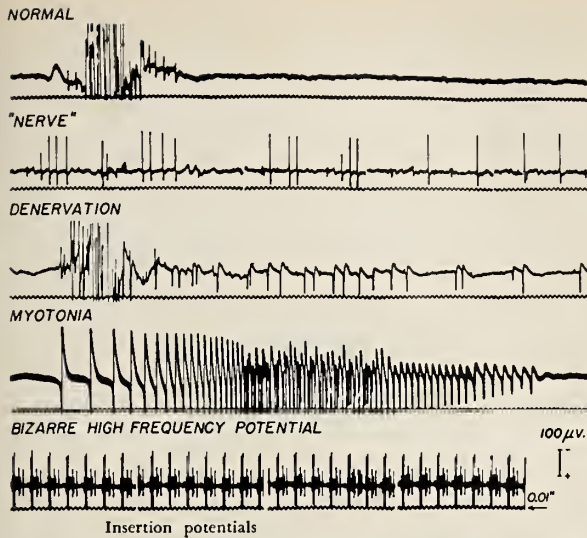


Figure 1.—Electromyographic recordings of normal, denervated and myotonic muscle. Delayed relaxation is exemplified by the prolonged persistence of electrical activity.

caused him to fall. The "tightness" of muscle was not affected by sudden exposure to cold temperatures and the patient's muscle power remained normal. By the age of 16 he was able to lift 100 pounds over his head. Over the years, muscle stiffness gradually worsened. The patient denied visual, sensory or other neurological symptoms. His scholarship in school was always above average. Past medical history and review of systems was unremarkable. Since the patient was an adopted child, family history was virtually impossible to obtain. The only known relative was a sibling who was said to be completely normal.

General physical examination was within normal limits. Neurological examination revealed an alert, oriented and cooperative boy with normal memory and intelligence. The results of examination of the cranial nerves were normal with the exception of the finding of lid myotonia: When the patient was asked to look suddenly at the floor after he had been staring at the ceiling, the upper lids remained elevated and relaxed slowly. Tongue, grip and percussion myotonia of other muscles was easily elicited. The patient's muscles were generally hypertrophied, but exhibited normal power and coordination. Reflexes were symmetrical and no pathological reflexes could be elicited. Sensory examination revealed normal findings.

The results of the following laboratory investigations were all within normal limits: hemo-

globin, white blood cell count and differential, sedimentation rate, serology, urinalysis, serum electrolytes, serum calcium, phosphorus, fasting and two-hour post-prandial blood sugar, total protein, protein and immuno-electrophoresis, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK). Chest films and electrocardiogram were normal. Slitlamp examination showed no evidence of cataracts. The electromyogram showed a somewhat increased insertional activity, no fibrillations, no positive sharp waves or fasciculations and a normal interference pattern. The typical "dive bomber" sound was obtained (Figure 1). Potassium loading with 7.5 grams of KCl failed to produce weakness.

Dilantin, 100 mg three times a day, was prescribed. Within two weeks after this therapy was begun the patient showed a remarkable decrease in muscle stiffness and myotonia.

It is unfortunate that a family history could not be obtained in the case of this patient. The presence of myotonia without paroxysmal or progressive weakness, the absence of wasting and the lack of any other stigmata of myotonic dystrophy (cataracts, baldness and testicular atrophy) and the negative potassium loading test confirmed the diagnosis of myotonia congenita. A somewhat atypical feature of this case was the fact that myotonia was not aggravated by exposure to cold.

*Dr. Dreyfus:* Thank you, Dr. Bhatt. Dr. Vijayan, would you review the various disease entities in which myotonia may be elicited?

*Dr. Vijayan:* One can identify three disease entities in which myotonia is a major clinical manifestation (Table 1). These are: (1) myotonia congenita, sometimes known as Thomsen's disease; (2) paramyotonia congenita of von Eulenberg; and (3) myotonic dystrophy. In addition, there is a group of muscle diseases associated with myotonia which may be placed into the general category of myotonia acquisita. The various myotonic syndromes are easily and readily distinguished on clinical grounds.

*Myotonia congenita.* As the term implies, this disorder is present at birth. Although it is transmitted by an autosomal dominant gene, it may have recessive characteristics. Affected infants may manifest a "strangled cry," and this may be associated with feeding difficulties. Developmental milestones are frequently delayed. In



TABLE 1.—*Diseases Associated with Myotonia*

<i>Type</i>	<i>Age of Onset</i>	<i>Mode of Inheritance</i>	<i>Prognosis</i>	<i>Associated Findings</i>
Myotonia congenita (Thomsen)	Birth	Dominant	Non-progressive	None
Paramyotonia (von Eulenberg)	Childhood, adolescence	Dominant	Non-progressive	Periodic paralysis
Dystrophia myotonica (Steinert)	Late adolescence and early adult life	Dominant	Progressive	Testicular atrophy frontal baldness cardiac involvement mental deficiency
Hyperkalemic periodic paralysis	Childhood to early adult life	Dominant	Improves with age	Paramyotonia
Polymyositis	Any age	None	Variable	Generalized collagen disease Neoplasia Skin rash

general, myotonia is diffuse, involving all of the voluntary muscles. As the patient develops and grows older, muscles may become hypertrophic and the myotonia tends to decrease in severity. Myotonia may worsen on exposure to cold while it improves with exercise, although in some cases it may be aggravated by exercise, a phenomenon referred to as "myotonia paradoxa." Generally speaking, myotonia is not associated with severe pain or cramps, as is the case in myopathy associated with a lack of myophosphorylase (McArdle's disease) and other enzymatic deficiencies. As a rule dystrophic features do not develop in patients with myotonia congenita and the disease runs a benign course.

**H**istopathological examination of muscle fibers shows diffuse hypertrophy. Except for large and elaborate end-plates, which are supposed to be characteristic of this condition, no specific pathological changes can be discerned. The muscle enzymes are not elevated in the serum, except in rare and severe cases, in which serum aldolase may be elevated.

Another disease entity associated with myotonia in infancy was described by Schwartz and Jampel in 1962.<sup>1</sup> This is a familial disorder characterized by myotonia, short stature, a variety of skeletal anomalies, especially hip dysplasia, and unusual facial and ocular abnormalities. Most of the afflicted children have diffuse muscular hypertrophy. The mode of inheritance of this disorder has not as yet been worked out.

*Paramyotonia congenita.* In this benign disease entity, the myotonia becomes evident on expo-

sure to cold. The distinguishing feature of this disorder is the occurrence of episodic flaccid paralysis similar to that seen in periodic paralysis. Most of the cases have associated hyperkalemia during the paralytic attacks and some investigators<sup>2</sup> consider hyperkalemic periodic paralysis and paramyotonia congenita to be one and the same disease entity. Myotonia tends to be restricted to the lids, the tongue, the face or the distal parts of the extremities. It is not uncommon to elicit a history of myotonia of the tongue precipitated by licking an ice cream cone. Dystrophic changes do not develop. The trait is transmitted in an autosomal dominant manner which has almost 100 percent penetrance in both sexes. No specific histopathological changes have been described.

*Myotonic dystrophy.* This disease tends to begin in adolescence or early adult life. The clinical presentation is quite variable from family to family and from generation to generation in the same family. Myotonic dystrophy may start with myotonia, then is followed in time by atrophy and weakness of muscles as well as by systemic dystrophic manifestations. Quite frequently the earliest muscles to be involved are those of the face and neck or the peripheral muscles of the extremities. Mild ptosis and lack of facial expression may be present for a long time before any other changes become evident. Since the masseter and the sternocleidomastoid muscles are commonly involved, the patient's neck may appear to be thin, with an exaggerated forward curvature sometimes referred to as "swan neck." Partial ptosis of the lids is almost always present and in

50 percent of cases the external ocular muscles are also involved. As the disease progresses, dysarthria and dysphagia develop due to involvement of the laryngeal and pharyngeal muscles. While myotonia can best be demonstrated in the thenar muscles by percussion or the "hand-grip test," it is electromyographically obvious in all the involved muscles. In the latter phases of the disease, at a point when muscle atrophy is extensive, clinical myotonia may no longer be elicited. Unlike myotonia and paramyotonia congenita, myotonic dystrophy is a progressive disease with a slow downhill course which leads to severe disability within 15 to 20 years from the onset.

**D**ystrophic manifestations in nonmuscular tissue consist of cataracts in 42 percent of patients, frontal baldness in 44 percent, testicular atrophy in 70 percent of males and a variety of sexual disorders in 64 percent of females.<sup>3,4</sup> A fairly large proportion of patients with myotonic dystrophy, and some of their unaffected siblings, have associated mental deficiency. Cardiac involvement is quite common and can be held responsible for sudden death. Electrocardiographic changes are present in 90 percent of cases in the late stages of the illness.

Although significant endocrine and metabolic changes have been described in association with myotonic dystrophy, no definite clinical correlation has been possible. In patients with testicular atrophy, the seminiferous tubules closely resemble those seen in Klinefelter's syndrome, but the nuclear sex chromatin pattern is normal. The various other changes frequently noted are a low basal metabolic rate, hypothyroidism, diabetes mellitus, reduced 17-oxy steroid excretion and increased levels of interstitial cell stimulating as well as luteotropic hormones. The latter changes are not observed with any degree of consistency. Alterations in the level of serum globulins have also been noted. In the majority of cases, gamma globulin is reduced and beta globulin elevated. Total protein values, on the other hand, are normal. It is of interest that the survival rate of radioactively labeled gamma globulin is shorter in patients with myotonic dystrophy than in normal persons<sup>5</sup>.

Histopathologically, changes observed in this disease are similar to those seen in other types of muscular dystrophy—scattered enlargement of fibers, degeneration and centrally placed sarco-

lemmal nuclei. The two characteristic pathological features commonly seen in this disease are: (1) prominent, long chains of centrally placed nuclei in an apparently intact muscle fiber, and (2) striated annulets or "Ringbinden" in transverse sections. These pathological changes are probably the result of reorientation of peripherally placed myofibrils from a longitudinal direction to one in which the fibrils encircle the fiber shaft. Similar changes have been observed in the contraction band of aging normal muscle, but they appear to be much more pronounced and frequent in myotonic muscle fibers. Striated annulets are thought by some to be caused by excessive irritability of the muscle fibers. Another distinctive pathological change is the presence of sarcoplasmic masses or regions of sarcoplasm in the center of the fibers, which are devoid of myofibrils.

*Myotonia acquisita.* In addition to the above-described syndromes, myotonia has been noted as a minor manifestation in other muscle diseases. Thus, it has been described in cases of polymyositis,<sup>6</sup> where it is transitory in nature, disappearing as the disease progresses. It has also been recorded in cases of progressive muscular atrophy and also in rare instances of polyneuropathy. The delayed relaxation seen in myxoedema does not have either the clinical or the electromyographic characteristics of myotonia and is therefore referred to as "pseudomyotonia."

**A**s was mentioned earlier, myotonia may be a feature of periodic paralysis. It has been consistently seen in association with the hyperkalemic form<sup>7</sup> of the disease. While myotonia is usually seen during episodes of weakness, sometimes it may be demonstrated only by electromyography. Myotonia has also been described in a case of hypokalemic periodic paralysis.<sup>8</sup>

Lastly, myotonia can be mistaken for a syndrome tentatively attributed to a reduction of muscle relaxing factor.<sup>9</sup> This entity is characterized by painless contraction and stiffness of muscles associated with electromyographic "silence" following exercise. Blood pyruvate and lactate levels before and after exercise performed under ischemic conditions are higher than in normal persons. Myophosphorylase activity is normal. Sarcoplasmic reticulum isolated from the muscles of such a patient reveals a decidedly reduced ability to take up calcium. This causes a delay



in relaxation and may be due to a deficiency of relaxing factor. In myotonia, slow relaxation is attended by visible and audible electromyographic activity.

*Dr. Dreyfus:* Thank you, Dr. Vijayan. I will now ask Dr. Bhatt to review for us the current pathophysiologic knowledge of myotonia.

*Dr. Bhatt:* It is perhaps best to begin by saying that pathophysiologically myotonia is as yet poorly understood. However, let us make an attempt to present a workable hypothesis based on available evidence.

To a considerable extent the experimental approaches to the understanding of myotonia have been helped by the availability of an animal model, a breed of goats native to certain parts of the southern United States that are subject to myotonia congenita.

As in all experimental neurology, some of the earliest methods of analysis were by the process of elimination. Procedures ranging from removal of the highest cortical centers to transection of peripheral nerves were found to have no effect on myotonia. Therefore, it was surmised that the disease involved structures distal to the nerve. It remained for acquisition of the knowledge of the mode and site of action of curare to exonerate the end-plate from the list of potential culprits. The study of individual neuromuscular junctions in myotonia has added further evidence that pre-synaptic mechanisms, end-plate potentials, acetylcholine sensitivity, and acetylcholinesterase activity are normal.<sup>10</sup> These findings localize the search for the origin of myotonia to the muscle fiber.

Before proceeding further with our method of analysis, it may be useful to recapitulate briefly some of the biophysical processes involved in muscle contraction. First, the surface membrane of the muscle is depolarized. This depolarization then spreads into the interior of the fiber by means of a transverse tubular system, causing depolarization of the sarcoplasmic reticulum, another system of tubules which stores calcium. Release of calcium ions from the sarcoplasmic reticulum activates muscle contraction. Released calcium interacts with tropomyosin, one of the muscle proteins, with the subsequent formation of bridges between the contractile protein actin and another protein, myosin. This set of events leads to contraction of the muscle fiber. Relaxa-

tion, on the other hand, is probably the result of calcium being "soaked up" by the sarcoplasmic reticulum.

The basic defect in myotonia has not yet been clearly elucidated. The most probable cause of the phenomenon appears to be some physiologic alteration in the muscle membrane which renders it unduly sensitive to electrical, chemical and mechanical stimulation. More specifically, there may be defective depolarization. Other mechanisms which have been postulated are an inordinate propensity for actin and myosin to maintain bridges, resulting in prolonged contraction, or a failure in calcium uptake by the sarcoplasmic reticulum, resulting in delayed relaxation. However, biochemical and ultramicroscopic studies of myotonic muscle have revealed that the latter two mechanisms are entirely normal.

In lower animals, two types of muscle are found: white and red. The former are responsible for twitch contraction—that is, they respond to stimuli by a quick contraction. They have a well developed sarcoplasmic reticulum and abundant glycolytic enzymes for their anaerobic metabolism. The red fibers respond in a slower and more sustained manner. They have a poorly developed sarcoplasmic reticulum and depend on oxidative enzymes. All human muscles are mixed. Muscles which have a preponderance of white fibers have sarcoplasmic reticulum characterized by high levels of calcium and a rapid rate of uptake of this ion. In myotonic dystrophy, the initial rate of calcium uptake is higher than normal while the total uptake remains normal. This suggests that red fibers are involved predominantly.<sup>11</sup> This fact has been substantiated by histochemical studies.<sup>12</sup>

Another way to study a clinical condition is to produce the entity in normal experimental animals by means of exogenous factors. Myotonia develops both in humans and in experimental animals when they are treated with certain inhibitors of cholesterol biosynthesis<sup>13,14</sup>.

The analogues of cholesterol which act by inhibiting the conversion of desmosterol (dehydrocholesterol) to cholesterol, tend to produce myotonia. These agents cause an increase in plasma desmosterol and a consequent fall in plasma cholesterol. On the other hand, agents which block the synthesis of mevalonic acid—a precursor of cholesterol—do not cause an increase in plasma

desmosterol; they reduce plasma cholesterol yet do not produce myotonia. Triparanol, a non-steroid compound which increases plasma desmosterol and which reduces plasma cholesterol, does not produce myotonia. Therefore, in order to be a myotonogenic agent, the drug must be a steroid which causes an increase in desmosterol and a decrease in cholesterol levels. The structure activity relationship of these compounds seems to reside in their specific dialkylamino substituted steroid nucleus. Sophisticated studies have shown that at least some of these myotonia producing agents have been incorporated into the lipid portion of the red blood cell membrane. Granted that it is a far cry from the red blood cell wall to the membrane of an isolated muscle cell, a beginning appears to have been made.

From the physiological point of view, the upstroke of the action potential representing depolarization of a muscle fiber is due to a sudden increase in sodium permeability, while the downstroke is caused by a combination of decreased sodium and an increase in potassium permeability. During depolarization the sodium leaks into the cell and potassium leaks out; therefore, anything which prevents either the exclusion of sodium or the intrusion of potassium may lead to persistent depolarization. A malfunctioning sodium pump could prevent normal sodium potassium exchange and result in a high intracellular sodium concentration and an elevated extracellular potassium concentration.

Certain studies carried out in human myotonic dystrophic muscle have shown that there exists no difference between the sodium pump efficiency relative to that of normal muscle, while there is a difference between the steady or resting membrane potentials of normal and myotonic dystrophic muscle, the latter being somewhat less negative.<sup>15</sup> The alteration in the steady-state transmembrane potential has not been substantiated in myotonic goats.

Another cause of repetitive activity in skeletal muscle is an increase in the membrane resistance. Studies in myotonic goats have shown that while the fiber capacitance and myoplasmic resistance are normal, the membrane resistance is two and one half times that of normal goat muscle membrane.<sup>16</sup> The increased membrane resistance could conceivably be due to a decreased potassium permeability bringing about an ionic im-

**TABLE 2.—Effective Therapeutic Agents for Myotonia**

Diphenylhydantoin (Dilantin®)
Procainamide (Pronestyl®)
Quinine sulphate
Adrenocorticotrophic hormone (ACTH)
Corticosteroids (cortisone)

balance which could cause myotonia. This is known to occur in denervated muscle. Denervation, however, is rarely part of the disease in which myotonia is present. No definite decrease in potassium permeability has been demonstrated. Lipidy and Bryant<sup>17</sup> suspect that in goat myotonia the permeability to chloride may be decreased. No such dysfunction has as yet been conclusively demonstrated in human myotonic muscle.

From the above it may be inferred that the defect, whatever it is, probably resides in the membrane. In myotonic dystrophy and myotonia congenita there is no abnormality of the intracellular or extracellular ionic concentrations. In hyperkalemic periodic paralysis, while at certain times changes in potassium concentration are present, the myotonia often persists in the period between attacks, during which ionic concentrations are normal. Therefore, it is more likely that, rather than being causally related, hyperkalemia and myotonia are either independent phenomena or stem from a common defect. It is also likely that the precise muscle membrane defect or defects responsible for myotonia may be different in each clinical entity in which the symptom is encountered.

*Dr. Dreyfus:* Thank you, Dr. Bhatt. Now that we have considered the clinical and the pathophysiological aspects of myotonia, a few words should be said about its treatment. Since it is generally believed that myotonia is caused by a biophysical abnormality of the muscle membrane, therapeutic agents which stabilize or hyperpolarize the membrane or drugs which alter the ratio of extracellular to intracellular ions might be expected to bring about symptomatic relief. Drugs which have been used successfully for myotonia include diphenylhydantoin (Dilantin®), procainamide (Pronestyl®), quinine and adrenocorticotrophic hormone (see Table 2). Of the various drugs used, Dilantin appears to be the most effective, the safest and the best tolerated. The mechanism of action of Dilantin in the treatment of myotonia remains essentially unknown. Experi-



mental evidence suggests, however, that the drug acts directly on the muscle fiber membrane by activating the sodium pump. The resultant extracellular sodium shift would tend to stabilize the membrane. Three hundred milligrams of Dilantin a day, given in divided doses, is effective, frequently without side effects of note. However, ataxia, bone marrow depression and proliferation of lymphoid tissue must be anticipated. Dilantin generally produces better results than does procainamide (Pronestyl®), which must be administered in large daily doses (3 to 4 grams) and which may produce unpleasant side effects such as insomnia, irritability, nausea and dyspepsia. In most patients, Pronestyl is more effective than is quinine. The latter, given orally, 500 to 1000 mg a day, frequently causes nausea, tinnitus, headaches and visual symptoms. Adrenocorticotrophic hormone and cortisone are of doubtful value. However, they may reduce myotonia by altering the ratio of extracellular to intracellular potassium or sodium. In addition steroids may slow up the inexorable progress of the destructive process of myotonia dystrophy.

More specific treatment of myotonia awaits the elucidation of basic pathophysiology.

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ACKNOWLEDGMENT: We wish to thank Dr. Ted N. Thompson for permitting us to examine and discuss his patient.

## TRADE AND GENERIC NAMES OF DRUGS

Dilantin® .....diphenylhydantoin  
Pronestyl® .....procainamide

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## VASOCONSTRICTORS IN SHOCK?

In the surgical patients you see in shock, both from volume loss and from sepsis, do you use vasoconstrictors at any time?

"During the early stages of shock, the normal physiology is one of increasing activity of the sympathetic nervous system. That means, among other things, increased heart rate and increased vasoconstriction. It would seem very unreal to me to give a vasoconstrictor under those circumstances. The body is doing the best it possibly can; and it doesn't really benefit from any help.

"On the other end of the spectrum, when we're in the stage where shock has been going for a long time, and we're now getting into that loose unhinging of all mechanisms, it's conceivable that one should infuse a vasoconstrictor to help support the pressure."

—WILLIAM R. DRUCKER, M.D., Toronto

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# Congestive Heart Failure After Acute Myocardial Infarction

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SLEISENGER:\* This morning Dr. Scheinman will discuss congestive heart failure after acute myocardial infarction.

DR. SCHEINMAN:† The precise definition of "heart failure" has eluded far more sophisticated students of cardiology<sup>1</sup> than I, and the term will not be belabored here. Instead, we shall focus on an easily recognized clinical syndrome occurring after acute myocardial infarction that is manifested by dyspnea, pulmonary congestion, and elevated left ventricular filling pressure, which may or may not be accompanied by right heart failure. This syndrome, congestive heart failure, is not an uncommon complication after acute myocardial infarction.

### Clinical Characterization

I should like to review briefly our experience with patients showing postinfarction pump failure. Over a period of three years a total of 368 patients were admitted to the coronary care unit at San Francisco General Hospital with the diagnosis of definite or probable acute myocardial infarction (Table 1). One hundred fourteen patients showed clinical manifestations of congestive heart failure but without cardiogenic shock (defined by a blood pressure below 80 mm of

mercury and signs of poor perfusion, including urine output of less than 30 ml an hour). Sixty-one of these patients had mild heart failure manifested by persistent bibasilar rales, dyspnea or S<sub>3</sub> gallop, while 53 had overt signs and symptoms of pulmonary edema.

In the absence of shock, there was no statistically significant difference in mortality between patients with or without either mild or severe heart failure. On the other hand, the combination of severe congestive heart failure (pulmonary edema) and shock carried a very poor

TABLE 1.—Incidence of and Mortality from Pump Failure in Patients with Acute Myocardial Infarction

	No. of Patients	Incidence (Percent)	Mortality (Percent)
Patients with definite or probable acute myocardial infarction . . . . .	368	100	22.01
Patients with postinfarction pump failure . . . . .	178	48	38
Mild congestive heart failure alone . . . . .	61	17	15
Severe congestive heart failure alone . . . . .	53	14	17
Cardiogenic shock (no severe congestive heart failure) . . . . .	35	10	66
Severe congestive heart failure and shock . . . . .	29	8	90

\*Marvin H. Sleisenger, M.D., Professor of Medicine.

†Melvin M. Scheinman, M.D., Assistant Professor of Medicine.



**TABLE 2.—Age Groupings of 368 Patients with and without Severe Congestive Heart Failure\***

Age (yr.)	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)
30-39 .....	1	5
40-49 .....	9	16
50-59 .....	24	31
60-69 .....	33	26
70-79 .....	26	16
80+ .....	7	6

\*For this and subsequent tables the designated percentage of patients for each parameter examined (e.g., age ranges) was derived by dividing the number of patients in the parameter group by the number of patients either with severe or with mild or no congestive heart failure.

**TABLE 3.—Incidence of Positive Previous History of 358 Patients with and without Postinfarction Severe Congestive Heart Failure**

Prior Positive History	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)	P Value*
Angina .....	28	38	NS
Myocardial infarction ..	38	27	NS
Hypertension .....	34	30	NS
Congestive heart failure	31	16	<.01
Diabetes .....	15	17	NS

\*P value was derived by chi square method in this and other tables; NS=not significant.

**TABLE 4.—Time from Onset of Symptoms to Hospital Admission in 368 Patients with and without Congestive Heart Failure**

Time (hr)	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)
0-3 .....	55	62
3-6 .....	11	9
6-12 .....	14	11
12-24 .....	11	2
24-72 .....	2	8
72+ .....	7	8

prognosis. In our experience, severe congestive heart failure and shock in a patient with acute myocardial infarction does not usually respond to medical therapy and these patients might well be considered as candidates for mechanical circulatory assistance or surgical intervention or both.

We found no statistically significant difference between the ages of patients with or without severe heart failure (Table 2) but there was a significantly higher incidence of a previous history of heart failure in the group with severe congestive heart failure (Table 3). The time from onset of symptoms to hospital admission

**TABLE 5.—Presenting Complaints in 368 Patients with and without Postinfarction Severe Congestive Heart Failure**

Complaint	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)	P Value*
Pressure or vise-like pains .....	25	47	NS
Dull pain .....	9	11	NS
Burning pain .....	4	10	NS
Sharp pain .....	11	13	NS
Dyspnea .....	60	19	<.01
Gastrointestinal symptoms .....	11	12	NS
Postcardiac arrest ....	9	6	NS
Coma .....	5	3	NS
Silent .....	5	5	NS
Nondescript symptoms. .	9	8	NS

\*P value was derived by chi square method in this and other tables; NS=not significant.

**TABLE 6.—Arrhythmias in 368 Patients with and without Severe Congestive Heart Failure**

Arrhythmia	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)	P Value*
Sinus tachycardia ....	53	29	<.01
Sinus bradycardia ....	11	15	NS
Atrial fibrillation ....	15	9	NS
Ventricular premature beats .....	66	54	NS
Ventricular tachycardia			
Primary .....	4	13	<.025
Secondary .....	21	5	<.01
Nodal rhythm .....	12	8	NS
Atrioventricular block			
First degree .....	18	8	<.05
Second degree .....	7	4	NS
Advanced .....	1	2	NS
Complete .....	7	5	NS

\*P value was derived by chi square method in this and other tables; NS=not significant.

was similar for both groups (Table 4). Patients with severe heart failure showed a significantly greater incidence of dyspnea as a presenting complaint and showed a significantly lesser incidence of severe oppressive precordial pain (Table 5).

Arrhythmias were very frequent in these patients (Table 6). The incidences of sinus tachycardia and secondary ventricular tachycardia were significantly higher in the group with severe heart failure. We found no statistically significant difference in the anatomic location of

**TABLE 7.—Area of Myocardial Infarction in 40 Patients with and without Postinfarction Severe Congestive Heart Failure Examined Post Mortem**

Area of Infarction	Severe Congestive Heart Failure (Percent)	Mild or No Congestive Heart Failure (Percent)
Anterior .....	41	39
Anterolateral .....	18	9
Postero-inferior .....	18	30
Apical .....	12	4
Septal .....	6	4
Subendocardial .....	6	0
Lateral .....	0	4
No Postmortem changes...	0	9

infarction found post mortem between the two groups (Table 7).

Objective hemodynamic measurements have clarified the significance of various clinical findings. Lassers, et al.,<sup>2</sup> for example, found a poor correlation between mean pulmonary capillary wedge pressure and diastolic heart tones, dyspnea or persistent basilar rales. All but one of his patients with a wedge pressure greater than 20 mm of mercury had diastolic gallop sounds, but many patients with normal pressures had the added sounds. There was good correlation between the mean wedge pressure and the radiographic findings in patients with pulmonary venous congestion or pulmonary edema. Similarly, there was good correlation between heart rate (in patients with sinus tachycardia) and mean wedge pressure.

### Pathogenesis

Obviously the single most important factor in the genesis of congestive heart failure after infarction is destruction of so much myocardium that the heart is unable to meet tissue needs at a normal filling pressure. The exact reason for the elevated left ventricular filling pressure is not known. Conceivably the severely infarcted heart depends upon the Starling<sup>3</sup> effect as a mechanism for raising cardiac output. In this instance the raised ventricular filling pressure would represent an augmented end-diastolic volume (and hence increased end-diastolic stretch).

Alternatively, extensive myocardial infarction may result in serious reduction in compliance<sup>4</sup> so that given increments in volume result in pronounced rises in pressure. The latter mechanism would not necessarily result in an augmented end-diastolic volume. The distinction between

these two mechanisms is more than merely academic; it has important therapeutic implications in the clinical management of these patients.

Myocardial infarction regularly results in areas of the myocardium that are either akinetic or dyskinetic.<sup>5</sup> These abnormal functioning units would be expected to produce serious adverse physiological effects.<sup>6</sup> For example, during isovolumic contraction, the poorly contractile areas of myocardium would be expected to result in an increase in the series elastic resistance. Similarly, in the course of ventricular systole blood would be regurgitated into the aneurysmal sac, serving to decrease stroke volume and to increase myocardial oxygen needs by increasing wall tension.<sup>7</sup> Finally, the aneurysmal areas may be the nidus for serious ventricular arrhythmias or thrombi.<sup>8</sup>

Congestive heart failure may occur as a result of papillary muscle dysfunction or rupture of either the ventricular septum or papillary muscle. The therapeutic implications of these lesions will be discussed later.

### Hemodynamic Abnormalities

Recent studies have clarified the hemodynamic changes seen in postinfarction congestive failure. The cardiac output is generally (but not always) reduced and, more significantly, the difference between arterial and mixed venous oxygen content is usually increased,<sup>9</sup> suggesting that the stroke output is insufficient to meet peripheral demands. The mixed venous or central venous oxygen saturation is usually less than 60 percent.<sup>10,11</sup> Left ventricular filling pressure and pulmonary artery, diastolic and wedge pressures are passively elevated,<sup>12</sup> but the central venous pressure may be normal.<sup>13</sup> Our initial report of normal central venous pressures in one-third of our patients with acute myocardial infarction complicated by pulmonary edema<sup>13</sup> has been substantiated by others.<sup>9,11</sup> These findings raise considerable doubt as to the validity of use of central venous pressure as an estimate of left ventricular filling pressure in patients with acute myocardial infarction.

### Therapy

The general principles of therapy for patients with acute infarction apply equally well to the subgroup with postinfarction congestive failure. Rest and relief of pain and anxiety are impor-



tant in decreasing myocardial oxygen requirements. Similarly, patients should be nursed in the sitting position to decrease venous return and hence cardiac work. Application of stockings to the mid-thigh level and appropriate leg exercises are probably of aid in promoting venous return and in decreasing the incidence of thromboemboli. The diet should be restricted in salt, as these patients have a strong tendency to retain sodium<sup>15</sup> and have been shown to have an elevation of steroid hormone levels.<sup>16</sup>

Cardiac arrhythmias are commonly seen in these patients and may produce further hemodynamic deterioration in a variety of ways.<sup>17</sup> For example, a patient with a slow heart rate may not be able to compensate with increases in stroke volume, or tachycardias may result in an inadequate diastolic filling period, or asynchrony between atrial and ventricular contraction may result in loss of the atrial transport function. Thus, these patients should be kept in a coronary care unit and prompt appropriate antiarrhythmic therapy should be instituted when necessary. Similarly the presence of hypoxia and acidosis should be sought by analysis of arterial blood and promptly corrected if found.

The role of digitalis in patients with acute heart failure remains controversial. Hemodynamic studies in patients on both ends of the power failure spectrum, namely mild heart failure or shock, show little, if any, objective hemodynamic evidence of improvement after digitalis therapy.<sup>18-20</sup> The broad intermediate group of patients with symptomatic heart failure appear to be benefited, but there are no hemodynamic studies to substantiate (or negate) this clinical impression. Patients with acute myocardial infarction are probably slightly more sensitive to digitalis than are normal subjects. Experimental studies in animals showed that the average intoxicating dose of digitalis is reduced by about one-third after myocardial infarction.<sup>21</sup> In addition, Cohn, et al.,<sup>20</sup> showed that the vasoconstrictor response to digitalis may precede the increase in contractility and may precipitate acute pulmonary edema in patients with cardiogenic shock. In summary, judicious use of digitalis is probably indicated in patients with acute myocardial infarction complicated by clearcut evidence of left ventricular failure.

The newer potent diuretic agents are a valuable addition to our therapeutic armamentarium

for patients with acute pulmonary edema. Our own studies using ethacrynic acid in patients with refractory acute heart failure showed that this agent results in prompt decreases in pulmonary artery pressure, while cardiac output remains unchanged.<sup>22</sup> Oxygen consumption tends to fall and arterial  $pO_2$  rises. These agents increase myocardial reserve, decrease pulmonary congestion and the work of breathing and result in better arterial oxygenation.

Glucagon is a polypeptide hormone produced by the alpha cells of the pancreas. Exogenous administration of this agent results in positive cardiac inotropic effects. These effects are thought to be mediated by increases in the intracellular concentration of adenosine 3' 5'-monophosphate and are not blocked by beta sympathetic blockade, nor are they diminished when digitalization has been carried out beforehand.<sup>23</sup> In addition, glucagon facilitates atrioventricular conduction and may be the drug of choice in patients intoxicated with beta adrenergic blocking agents.<sup>24</sup> Cardiac arrhythmias have not been associated with this drug.<sup>25</sup> The relatively few studies of this drug in patients with postinfarction myocardial failure showed differences in effectiveness of this agent.<sup>26,27</sup>

Dopamine is the biochemical precursor of norepinephrine and produces positive cardiac inotropic effects associated with variable effects of systemic resistance.<sup>28</sup> It has the unique property of selectively increasing renal blood flow by direct arterial vasodilation.<sup>29</sup> In one report, use of dopamine resulted in insignificant natriuresis in patients with refractory heart failure.<sup>30</sup> There are few reported studies of the use of this drug in patients with acute myocardial infarction.<sup>31,32</sup>

The circulation may be mechanically supported by reducing the volume work of the heart by venoarterial or left atrial bypass<sup>33</sup> or by decreasing pressure work of the heart by means of counter pulsation.<sup>34</sup> Counter pulsation may either be achieved by mechanical removal of blood during systole and replacement during diastole or by phasic intra-aortic balloon compression.<sup>35</sup>

Surgical repair of ventricular septal<sup>36</sup> or papillary muscle rupture<sup>37</sup> in patients with acute myocardial infarction has been reported. Infarctectomy<sup>38,39</sup> or coronary revascularization<sup>40</sup> or both in the acute phase of acute myocardial infarction are purely experimental.

## Summary

The mortality rate for acute myocardial infarction complicated by severe pump failure is very high. Therapy should be directed toward correction of electrolyte and acid-base disturbances, volume deficits and cardiac arrhythmias. Digitalis and diuretic agents are indicated in patients with severe heart failure and isoproterenol and/or norepinephrine in patients with cardiogenic shock. The clinical effectiveness of glucagon and dopamine, two newer inotropic agents, has not fully been evaluated. Similarly, surgical intervention in the form of infarctectomy or acute coronary revascularization still remains experimental.

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# Important Advances in Clinical Medicine

## *Epitomes of Progress -- Urology*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Urology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.*

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### Drip Infusion Pyelography in Renal Injuries

Injury to the urinary tract following blunt or penetrating abdominal trauma usually presents as hematuria and requires immediate diagnostic evaluation. Frequently, standard dose urograms are inconclusive and recourse to scans, retrograde pyelography and angiography is required. Clear delineation of the entire urinary tract can be obtained with drip infusion pyelography even in emergency circumstances. Through an 18-gauge needle, one ml of 50 percent sodium ditrizoate per pound of body weight mixed with

an equal volume of 5 percent dextrose in water is rapidly infused intravenously (300 ml in 6-10 minutes in adults). An optimal nephrogram is seen at ten minutes and maximal filling of the entire collecting system is normally apparent at 25 minutes. Laminography can be effectively applied to demonstrate suspicious areas and further contrast studies predicated by the anatomic lesions revealed. The technique is applicable in moderate renal failure and is especially useful in pediatric injuries. The presence of anuria is a relative contraindication and the procedure is not advised in myeloma.

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## Chronic Bacterial Prostatitis and the Problem of Antibiotic Diffusion

Chronic bacterial prostatitis, caused by sensitive Gram-negative organisms, is a major source of relapsing urinary tract infection in men. Although appropriate antibiotics readily sterilize the urine, the bacteria persist in the prostatic fluid because most antibiotics do not diffuse from plasma into the fluid. After drug therapy is discontinued, these persistent prostatic bacteria eventually reinfect the bladder urine.

Studies in dogs have shown that even with exceedingly high plasma levels of various antibiotics, there was little or none in the prostatic fluid. Only the basic macrolides (erythromycin and oleandomycin) were concentrated in prostatic fluid (2 to 3 times the plasma level). The basic macrolides, unfortunately, are generally ineffective agents against Gram-negative organisms that cause bacterial prostatitis.

The diffusion of any drug across biological membranes depends upon (1) the lipid solubility of the drug, (2) the dissociation constant (pKa) of the drug, and (3) the degree of plasma protein-binding of the drug. Only lipid-soluble drugs with minimal binding to plasma proteins and with favorable pKa values diffuse from plasma into prostatic fluid. Since most antibiotics that are effective against Gram-negative bacteria do not favorably meet these criteria, the cure of chronic bacterial prostatitis is rarely achieved. The ideal drug, theoretically, would be a base with a pKa value of at least 7.4, with a high degree of lipid solubility, and with minimal binding to plasma proteins.

EDWIN M. MEARES, JR., M.D.

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## Dependability of Renin in the Diagnosis of Renal Hypertension

Assay of plasma renin activity is gaining wide acceptance because there is generally a good correlation between plasma renin activity assay of the individual renal venous effluent and the diagnosis and prognosis of renal hypertension. While renin assay is an imperfect laboratory method at present and will undoubtedly be supplanted by radio-immunoassay of angiotensin in the future, it is sufficiently reliable to warrant use in all patients suspected of having renal hypertension. We do not believe that assay of peripheral venous blood for renin activity is dependable as a screening test but when blood from each renal vein is analyzed and a ratio of 1.5 to 1 or greater between the ischemic and contralateral kidney is found, considerable reliance can be placed on the method. Correlation has been found between renin assay ratios and the results of reconstructive or ablative operation in approximately 90 percent of cases. Assay of divided renal vein activity has gained better acceptance as a predictive test than have divided kidney function tests. In equivocal cases, divided kidney function tests may provide additional useful information.

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## Treatment of Undescended Testes

Treatment of an undescended testis before age of six is recommended. Three to five percent of children under one year of age have undescended testes. This may be associated with other urological anomalies. Most testes which remain undescended after age six undergo progressive functional loss which is irreversible after pu-



berty. Descent to the scrotum is necessary to provide the testis with the proper temperature environment to allow spermatogenesis. Androgen production is not affected.

Gonadotropic therapy of 10,000 International Units, in divided doses, over one to six weeks, given before the age of five, may be effective in 25 percent of cases, especially cases of bilateral undescended testes.

Surgical correction is indicated by the age of six to prevent progressive atrophy. Ninety percent are associated with inguinal hernia. There

is a greater incidence of malignant disease in undescended testis (20 to 50 times the norm). It is not clear that orchiopexy does anything to prevent this problem, other than place the testis where it can be observed. Psychologic and cosmetic needs must also be considered.

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## Some Lessons from the Medi-Cal Crisis

EACH MEDI-CAL CRISIS AS IT COMES along prompts another look at the relationships of medicine with government. A crisis develops when the quantity and quality of care which people expect (and to which they are deemed entitled by law) costs more than the state is willing to pay for the numbers of people it has declared to be eligible to receive care under the Medi-Cal program. The realistic solution is quite simple. The state should either reduce the numbers of persons eligible for care, or increase the funding for the program, or both. But usually neither of these logical approaches is politically palatable, so other alternatives are apt to be tried. These other alternatives seem somehow always to deprive patients of medical services. When either the quantity or quality of needed services becomes reduced by law or by fiat not only havoc but injustices are created. The further these unhappy alternatives to a realistic solution are pursued, the worse becomes the problem and the greater the suffering and the injustices to the poor patient and often the poor providers as well.

For some years the California Medical Association has studied some of the problems which have developed when governments become involved in personal health services on a large scale. In 1965 the Bureau of Research and Planning<sup>1</sup> and in 1967 the Committee on the Role of

Medicine in Society<sup>2</sup> called attention to experience elsewhere. It is in the nature of governments to fund health care services inadequately in the first place, and then to try to reduce the costs even further. Medicine on the other hand advocates that there be whatever funding is necessary to provide the quantity of services needed and to maintain and improve their quality. More often than not the struggle is an uneven one and the poor patient is its innocent, hapless and often helpless victim.

The cited report of the Committee on the Role of Medicine in Society went on to compare the basic strengths of government and medicine in health care. The power of government's position was seen to lie in (1) the legal determination that health care is a right of all citizens, (2) provision of financial support for health care through tax funds, (3) responsibility to exercise supervision and control over expenditures of public funds, and (4) the police power upon which all the resources and activities of government are ultimately based. The strength of medicine's position was to be found in (1) the essential nature of its services, (2) its expert knowledge of what is involved in patient care, (3) the importance of the skill and motivation of the physician to the quantity and quality of care rendered, (4) the need for freedom and incentives rather than restrictions if there is to be either quality or efficiency, and (5) a tacit public recognition that it is often better to have the physician and health professional working for the patient rather than for the government. The strengths of government's position are therefore firm and quite tangible. They are founded upon law, directed toward the "public interest,"

<sup>1</sup>Professional problems associated with federalized health care abroad—Socio-Economic Report of the California Medical Association Bureau of Research and Planning, Vol. 5, No. 11, Oct. 1965. Calif Med 104:146-152, Feb 1966

<sup>2</sup>A new relationship with government and others—A Report by the California Medical Association Committee on the Role of Medicine in Society. Calif Med 107:109-114, Aug 1967



and in the final analysis are enforced by compulsion. Medicine's strengths on the other hand are more fragile and often quite intangible. They rest upon the skill, motivation and unique competence of the health professional, are directed to the needs of the individual who is or may become a patient, and derive their public support from good performance which is understood and appreciated.

The medical profession has yet to perfect the skills needed to bring these less tangible strengths of medicine fully to bear upon the decision processes in the social, economic and political aspects of government involvement in health care. The Fourth Progress Report of the Committee on the Role of Medicine in Society (1968)<sup>3</sup> concerned itself in part with how this might be approached. It noted that it is public opinion which finally decides all the important public issues, whether in medicine or in government. It further noted that so far this fact has been better understood by government than it has by medicine. Medicine needs to develop a new and vastly improved technology for its advocacy of quality, quantity and efficiency in health care, if it is to gain the full understanding and active support of public opinion. There have been some beginnings and some accomplishments. But much more is needed. New and expanded social tactics of communication and involvement should be developed and used. New and more effective tactics to bring economic pressures to bear in various situations may soon be needed, and studies of how this might be done should be begun immediately. And much more sophisticated political tactics with far greater emphasis on involvement with others of like purposes and with much more effective use made of medicine's knowledge and expertise in patient care are necessary. These kinds of skills should be developed soon and put to use in the interest of both the patient and an all too often uninformed or misinformed public. It is already getting late.

The present Medi-Cal crisis will find some kind of resolution. But a permanent solution to the underlying problems is unlikely. The basic issues will be around to plague government-financed health care plans for a very long time to come. One fundamental issue, and sure to be a recurrent

one, is whether government programs are to continue to be patient-oriented or will they become bureaucrat-oriented. It already seems all too obvious that if the needs of the patient are to remain the central focus, there must be a strong advocate of these needs. Medicine can and should be this advocate. It alone has the technical knowledge of what is needed. To fulfill this role and responsibility, it will be necessary for the profession to develop those social, economic and political skills which will make the fragile and intangible strengths of medicine powerful enough to hold their own with the firm and very tangible strengths of government in the decisive arena of public opinion, where the public issues of both medicine and government are ultimately resolved.

Are there not some important lessons to be learned from this Medi-Cal crisis?

## Myotonia—A Different Point of View

THE INTERESTING TOPIC of myotonia has been presented in a Specialty Conference by members of the Department of Neurology at the University of California, Davis, published elsewhere in this issue. This editorial will present another classification of this group of disorders with speculations concerning pathogenesis.

The electrophysiological basis of myotonia is a repetitive, decrescendo and decelerating discharge of muscle fibers following voluntary contraction or stimulation by the motor nerve, percussion, or an electrode. Clinically it is a prolonged muscle contraction lasting several seconds or so. Myotonia is only a symptom or physical sign. Rather than classify "the myotonias," it is preferable to list the diseases in which myotonia is found:

1. Clinical myotonia
  - a. myotonia atrophica ("myotonia dystrophica")
  - b. myotonia congenita

<sup>3</sup>A role for medicine in a new era of health care—Fourth Progress Report of the California Medical Association Committee on the Role of Medicine in Society. Calif Med 108:311-315, 388-395, April & May, 1968.

- c. paramyotonia-adynamia complex — includes paramyotonia congenita and adynamia episodica hereditaria ("potassium-provoked periodic paralysis" or "hyperkalemic periodic paralysis, idiopathic")
- d. hypokalemic periodic paralysis, idiopathic
- e. chondrodystrophic myotonia<sup>1</sup>
- 2. Electromyographic myotonia only — occasional cases
  - a. denervation<sup>2,3</sup>
  - b. acid maltase deficiency (Pompe's disease)<sup>4</sup>
  - c. diazacholesterol<sup>5</sup> or 2,4-dichlorophenoxyacetate (2,4-D)<sup>6,7</sup> intoxication
  - d. polymyositis/dermatomyositis

Myotonia congenita is the disease presenting the most prominent and generalized form of myotonia. The initial muscle power may be slightly weak, but after the patient takes a few "warming-up" movements the strength becomes normal or better. These patients do not have attacks of episodic flaccid weakness spontaneously nor is weakness provoked by up to 10 gm of KCl orally.<sup>8</sup>

Paramyotonia congenita has lesser generalized myotonia, which is often evident from infancy (a cold washcloth can bring out myotonia of face and eyelids of the baby). Myotonia in all myotonic diseases is worsened by cold. Cold-provoked episodic flaccid weakness is more characteristic of paramyotonia. There was uncertainty initially about the relation between paramyotonia congenita and adynamia episodica hereditaria, but subsequently paramyotonia patients were shown to have potassium-provoked weakness,<sup>8,9</sup> and myotonia, sometimes in the eyelids only, was found in adynamia patients.<sup>10</sup> It seems to this reviewer that paramyotonia and adynamia represent two extremes of one disorder, the former having more myotonia and less episodic weakness than the latter. To test for potassium-provoked weakness, we give 5, 7.5, and 10 gm oral KCl (68, 101, and 135 mEq) on successive days until a response is obtained; the electrocardiogram is monitored during the test. Since the serum potassium is often not above the normal range during a spontaneous attack of weakness,<sup>10</sup> we prefer to call the disease "potassium-provoked" rather than "hyperkalemic" periodic paralysis. At one time, it was thought that eyelid myotonia could be used to distinguish adynamia from hypokalemic periodic paralysis. Subsequently some cases of clearly documented hypokalemic periodic paralysis were shown to

have clinical eyelid myotonia, indicating that this is not a reliable differentiating sign.<sup>11</sup> Myotonia is seen in only occasional cases of hypokalemic periodic paralysis and only in the eyelids.

Electromyographic (EMG) myotonia is seen in several disorders as noted above. The term "myotonia acquisita" has been applied to them. It is a misleading term, its Greco-Latinism suggesting a disease rather than simply the denotation of an acquired physical sign. I prefer it be dropped, and for another reason. The myotonia of myotonia atrophica, myotonia congenita and both types of periodic paralysis can also be "acquired" or at least noticed in childhood, or even young adulthood in the first.

There are several clinical phenomena of prolonged muscle contraction which resemble myotonia and must be differentiated from it:

1. Painful contracture after repetitive exercise, no rise of blood lactate—seen in abnormalities of glycogen metabolism, *viz.* phosphorylase deficiency (contracture electrically silent)<sup>12</sup> and phosphofructokinase deficiency (contracture not studied electrically)<sup>13,14</sup>

2. Electrically silent contracture (no mention of pain) after single contraction, normal rise of blood lactate, a congenital familial disease<sup>15,16</sup>

3. Electrically silent painless contracture after strong exercise, normal rise of blood lactate—one report of decreased ability of sarcoplasmic reticulum to accumulate calcium ions<sup>17</sup>

4. Electrically silent delayed relaxation of tendon reflex in myxoedema—caused by a defect of myofiber, probably of contractile mechanisms rather than of cell membrane<sup>16</sup>

5. Massive rigidity associated with malignant hyperthermia during and following general anesthesia—possibly a myofiber defect; one report of impaired calcium uptake by sarcoplasmic reticulum<sup>18</sup>

6. Syndrome of continuous muscle activity—caused by spontaneous discharge of the terminal portions of the lower motor neuron axon; this appears clinically as myokymia, and on EMG as trains of continuous motor unit activity; patients also have hyperhidrosis and elevated basal metabolic rate but normal thyroid function;<sup>2,19,21</sup> they usually do not have true myotonia; are responsive to diphenylhydantoin, carbamazepine, and acetazolamide

7. Cramps, consisting of high frequency trains of discharges of motor units—occur occasionally in normal muscle and more often in diseases of denervation



8. Tetany, in hypocalcemia — attributed to hyperexcitable peripheral nerve fibers<sup>16</sup>

9. Tetanus, from bacterial exotoxin—attributed to suppression of inhibitory synaptic action in the spinal cord<sup>22</sup>

10. Stiff-man syndrome — spontaneous prolonged contractions of central origin<sup>23,24</sup>

11. Spasms from black widow spider bite—site of action unknown<sup>16</sup>

12. Dystonia — spontaneous slow tonic contractions of cerebral origin, with “diseases of basal ganglia,” e.g. dystonia musculorum deformans

13. Rigidity — continuous muscle activity of cerebral origin, with “diseases of basal ganglia,” e.g. parkinsonism

14. Spasticity — spontaneous prolonged contractions and “stiffness” of central origin, with diseases of the corticospinal tracts.

Myotonia atrophica (or myotonic atrophy) is the most prevalent disease manifesting myotonia, and, in fact, is one of the most prevalent neuromuscular disorders. The term “myotonia atrophica,” actually one of the original names of the disease, is preferred as a more literal description of the disease than the currently nearly universally used term “dystrophica myotonica” (or “myotonic dystrophy”) of which the word “dystrophy” implies an hereditary disorder of the myofiber which is not secondary to neural involvement.

Myotonia atrophica is a slowly progressive multisystem disease, which includes involvement of the neuromuscular system, ocular lens, scalp hair follicles, and testes. One apparently unique metabolic abnormality has been identified, a short half-life of serum IgG due to hypercatabolism (without complex cryogels),<sup>25</sup> which is the basis of the low serum IgG. There is also an unusual hyperinsulinism without concomitant hypoglycemia.<sup>26,27</sup> The relation of the metabolic abnormalities to the various organ involvements is unknown. We will concern ourselves with the pathogenesis of the muscle weakness, atrophy and myotonia of this disease.

I propose that the muscle involvement in myotonia atrophica is secondary to chronic lower motor neuron (LMN) involvement and thus the disease is a form of neuropathy (used simply to designate a disease of all or part of the LMN) and not a myopathy. Normally the LMN exerts a number of influences on the several hundred muscle fibers (myofibers) it innervates. These LMN-to-myofiber influences can be thought of as “factors”

which, for purposes of discussion, are considered to be single and separate.<sup>28</sup> The proposed factors each might be chemically different or related to different patterns or amounts of release of a fewer number of substances. The excitatory factor is acetylcholine. The nature of the postulated trophic factor(s), which maintains myofiber health, diameter, and distinct histochemical type, is unknown. (Perhaps a separate trophic-type factor is responsible for maintaining the histochemical type.) The inhibitory “factor” is postulated to be that influence which keeps an innervated myofiber from discharging spontaneously, that is, from generating fibrillation potentials, as is characteristic of denervated myofibers; its nature is unknown. These factors or their metabolic support system probably are manufactured in a LMN soma and travel in the tide of axoplasmic flow down to its several hundred axon endings. It is proposed that in different diseases the LMN can react with different partial abnormalities, that is, with quantitative or qualitative abnormalities of axoplasmic flow, or both.

Evaluations of the findings in myotonia atrophica in support of this proposed pathogenesis are as follows. The exclusive early muscle lesion is myofiber atrophy without necrosis or phagocytosis.<sup>29-31</sup> In most instances it preferentially affects type I muscle fibers (low in myofibrillar ATPase and phosphorylase high in succinate dehydrogenase, and typed by the first reaction) but in some patients both fiber types are atrophic.<sup>29-31</sup> This atrophy more closely resembles atrophy due to loss of nerve supply than the changes of Duchenne pseudohypertrophic muscular dystrophy (postulated by us to be due to a blood vessel malfunction),<sup>32,33</sup> limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, or oculopharyngeal muscular dystrophy.<sup>34</sup> In more advanced myotonia atrophica, the muscle shows very atrophic fibers, sometimes in groups, clumps of pyknotic nuclei, infrequent necrotic fibers, some hypertrophied fibers, and sometimes slight endomysial connective tissue increase in the more severely affected regions, thus closely resembling what is seen in mid to later stages of neurogenic atrophy.<sup>29-31</sup> Even the multiple internal nuclei of myofibers seen in all stages of the disease conceivably are compatible with a form of neurogenic pathogenesis since they too occur, though not so abundantly, in ordinary chronic denervation. Sarcoplasmic masses, which are usually peripheral

with ring myofibrils just central to them,<sup>29,35</sup> are sometimes seen in myofibers of more severely involved muscle. They too are compatible with the proposed long-standing mild reduction of neural trophic factor, allowing some myofibers to undergo a sort of peripheral degeneration to form the sarcoplasmic masses and, it is proposed, some peripheral myofibrils to break and be pushed by repeated contractions to a ring position—because such peripheral degeneration of milder degree is sometimes seen by electronmicroscopy in experimentally denervated myofibers.<sup>31</sup> Ring myofibrils, as well as snake-coil myofibrils, which seem to be formed in a somewhat similar way, can be found in experimentally denervated muscle.<sup>31,36</sup>

Like chronic neurogenic atrophy, the “muscle enzymes” (SGOT, SGPT, LDH, CPK, and aldolase) are not significantly elevated in myotonia atrophica except for occasional mild increase of CPK,<sup>31</sup> contrasting with what is seen in active myopathy. In myotonia atrophica there are prominent abnormalities of motor nerve endings shown with methylene blue staining.<sup>37,38</sup>

The EMG pattern shows motor unit action potentials of short duration and small amplitude, and units firing more abundantly for a given amount of work. This pattern is usually erroneously called, without further qualification, “myopathic” because it is typically seen in Duchenne muscular dystrophy and certain other myopathies. Preferably it should be given a descriptive, non-diagnostic name, such as a “SSAP” (short, small, abundant potentials) pattern. In Duchenne muscular dystrophy and certain other myopathies it is attributed to loss of some myofibers from all motor units (a motor unit is one LMN and the several hundred myofibers innervated by it) leaving a normal total number of units but each with numerically reduced myofiber content. Such a reduced unit is less than normally efficient and therefore more units must fire to achieve a given amount of work. But it is logical that any disease affecting neuromuscular transmission of some but not all of the myofibers within each motor unit, or affecting only some of the prejunctional distal axonal twigs of each motoneuron “tree,” theoretically ought to also give a SSAP pattern. Just as when the flow of sap in a tree diminishes in autumn and some of the leaves fall before others (the most distal leaves fall first in sugar maples), it is proposed that when the LMN soma does not adequately nourish some of the axon tips in myotonia

atrophica, corresponding myofibers within each motor unit atrophy and eventually fail to respond to motor nerve firing (perhaps because of failure of axon tips to conduct) and thus cause an SSAP pattern. Another mechanism possibly contributing to the SSAP pattern in some patients is the selective atrophy of their type I myofibers.<sup>39</sup>

Clinical myotonia is a repetitive discharge of many myofibers. From an individual myofiber the individual EMG wave forms of myotonia usually are indistinguishable from fibrillation potentials or positive sharp waves, both characteristic of a denervated myofiber. The myotonia waves also look like denervated fiber activity with intracellular microelectrodes.<sup>10</sup> A similar repetitive discharge was recorded from individual myofibers of chick embryos growing in tissue culture without nerve.<sup>11</sup> The myotonic potentials are generated from the abnormally labile myofiber membrane, but normally the nerve controls the stability of that membrane. We propose that a decrease of inhibitory influence (“inhibitory factor”) from the LMN to muscle allows manifestation of myotonia.<sup>28</sup> “Pseudomyotonia” is the EMG term applied to a myotonia-like train of repetitive potentials that end abruptly rather than by decrescendo. The individual potentials are like the initial ones of myotonia. The distinction between pseudomyotonia and myotonia is probably not significant; both are likely to be caused by a very similar or the same defect of the myofiber membrane. We postulate that both are due to defective neural inhibitory factor. Pseudomyotonia, and sometimes true myotonia, can be seen in denervation. It is not known whether the myotonia in acid maltase deficiency is related to the known LMN soma abnormality<sup>12</sup> or myofiber abnormality, or both, of that disease. The pathogenesis of experimental myotonia induced by diazacholesterol and 2,4-D is not yet known. Polymyositis and dermatomyositis can have involvement of nerve endings histologically.<sup>37</sup>

Usually the motor nerve conduction time is normal in myotonia atrophica, which is compatible with preserved motor axon conduction function in the presence of decrease in only some of the neuronal factors to muscle.

The cerebrospinal fluid sometimes shows slightly or moderately elevated protein.<sup>31,43</sup> In many cases there is a mild aberration of thinking and sometimes frank retardation or dementia.



More advanced cases may have dilated cerebral ventricles.<sup>44</sup> These all point to some type of central nervous system involvement in myotonia atrophica. The motor nerves and motoneuron somas in the anterior horn of the spinal cord have not been considered to be morphologically abnormal, although newer techniques of histochemistry and electronmicroscopy have not been applied. Nevertheless, the motoneurons could be functionally abnormal while retaining a normal morphologic appearance.

The neuromuscular manifestations of myotonia atrophica are compatible with a chronic, neurogenic pathogenesis, which we prefer rather than a myogenic one. We propose that the disease is basically a chronic, partial defect of neuronal influence on muscle, mainly of neuronal trophic factor and inhibitory factor, with lesser defect of excitatory factor function. The defect is associated with abnormalities in distal portions of some axonal tips of each motor unit, which in turn may stem from abnormality of the motor neuron soma; this would be a mechanism similar to diminished axoplasmic flow induced by the neurotoxin acrylamide.<sup>45</sup> Perhaps the defect usually involves type I motoneurons more severely, though it could also be related to a greater susceptibility of type I myofibers to the abnormality. There is no basis for suggesting whether such a proposed LMN involvement is due to an inherited defect of LMN metabolism or the LMN metabolism is affected adversely by abnormality of another tissue which produces a detrimental influence or fails to provide a necessary influence required by the LMN. The implication of this neurogenic hypothesis for the neuromuscular involvement of myotonia atrophica is that the LMN and influences upon it must be studied rather than the muscle, which is viewed as a passive victim of effete neurons. It is concluded that myotonia atrophica is mainly a form of neuropathy, not a myopathy or muscular dystrophy. Whether there is a minor element of myopathy too is perhaps a possibility, but according to this hypothesis it is not the major pathogenesis.

If myotonia atrophica might be due to abnormality of neural influence on muscle, we must consider that myotonia congenita also may be, but caused by an abnormality involving a preferential loss of neural inhibitory factor (to release myotonia) rather than trophic factor. There is no myofiber atrophy early in the disease, though

later there may be atrophy of scattered fibers. Finally, the possibility of a neuropathic element, perhaps as a minor aspect of the pathogenesis, must be raised in potassium-provoked and hypokalemic forms of periodic paralysis, both of which can have some myotonia. The hypokalemic periodic paralysis typically has myofiber atrophy, roughly proportional to the duration and severity of disease.<sup>46</sup>

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## Diagnosis and Treatment of Pemphigus

THE REVIEW ON "Recent Advances in the Diagnosis and Treatment of Pemphigus" by Newcomer and Landau printed in this issue emphasizes the important effects of the discovery of circulating antibodies in pemphigus and in bullous pemphigoid. The etiologic concepts of these diseases as well as diagnosis and treatment have been affected.

With regard to etiology, the authors cite the available evidence indicating that the antibodies might be the cause of the disease in pemphigus and bullous pemphigoid. Although many factors speak in favor of this concept, the ultimate proof for it—namely, the passive transfer of the disease by means of its antibodies—may never be attained. Still, it can be said that lesions analogous to those of pemphigus vulgaris have been reproduced in animals by the experimental production of intercellular antibodies in such animals. Also, in addition to the evidence cited by the authors, it would seem that the favorable results obtained with methotrexate in the treatment of both pemphigus and bullous pemphigoid favor the concept of autoimmunity as a causative factor. In addition, the occasional coexistence of pemphigus with other immunological disorders, such as lupus erythematosus, rheumatoid arthritis and myasthenia gravis, indicates pemphigus too may be an autoimmune disorder, even though in most instances the additional immunologic disorder coexisting with pemphigus is silent and evident only by laboratory tests.

The diagnostic value of the demonstration of "antiepithelial" antibodies in pemphigus and of "basement zone" antibodies in bullous pemphigoid is considerable since these antibodies are specific for pemphigus and bullous pemphigoid, respectively. With adequate controls it is possible to avoid false positive results such as were obtained by the authors when fortuitously they used as substrate the esophagus of a rhesus monkey possessing blood-group-B substance. This resulted in fluorescence when serum from patients having anti-B isohemagglutinins in their blood was tested.

There is, however, a drawback in the antibody determination method for diagnostic purposes in that it may give negative results in the early stage of pemphigus or bullous pemphigoid when only a few lesions are present. Possibly, with improvement of the technique and the substitution of peroxidase-labeled antibodies for fluorescein-labeled antibodies, the incidence of false negative results can be reduced in the future. However, as was pointed out by the authors, it actually is not necessary to use indirect immunofluorescent testing for routine diagnostic purposes, since in most instances histologic examination is adequate for diagnostic clarification. Also, histologic examination enables one to dif-



ferentiate between pemphigus vulgaris and pemphigus foliaceus which, on indirect immunofluorescent examination, are indistinguishable.

Newcomer and Landau rightly emphasize that, even though there often is a correlation between the antibody titer and the severity of the disease, it is inadvisable to use determinations of the antibody titer as a guide for therapy. The clinical state of the patient is the only reliable guide.

They also point out that the greatest value of methotrexate in the treatment of pemphigus vulgaris lies not in the fact that occasionally in early cases it can completely replace prednisone, but rather that after the initial massive treatment with prednisone, the addition of methotrexate to the maintenance dose of the corticosteroid usually permits a gradual reduction in the maintenance dose and an earlier discontinuance of it. By reducing the incidence of serious and often fatal side effects of prednisone, methotrexate, particularly in patients with pemphigus vulgaris, has greatly improved the results of treatment over those obtained with prednisone alone and has further improved the prognosis of pemphigus vulgaris which at one time was almost always fatal.

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## "Right On!"

IN HIS "CONSIDERATIONS in Devising an Over-all Health Plan" submitted to the Department of Health, Education, and Welfare, and reprinted elsewhere in this issue, Dr. Russell Roth, the Speaker of the American Medical Association House of Delegates, is "right on." This concisely reasoned, thoughtful and accurate statement should not only be read, but carefully studied by practicing physicians, medical educators, health care planners, payors, providers, consumers and any others who may be in positions of influence with respect to the present health care "crisis" in the United States, or in California for that matter. Above all it should be read and pondered by legislators and other government officials who so often seem to create more problems than they solve by their no doubt well-intentioned legislative and administrative actions.

If Dr. Roth's "Considerations" should perchance be heeded by those in positions of power and influence in government and elsewhere, it could mark the beginning of what must be done if the health care problems of this nation are ever to be solved.

The AMA is to be congratulated upon having in its Speaker a spokesman of this caliber.

## THE PAIN OF BRAIN TUMOR

Would you describe the characteristics of head pain due to a brain tumor or increased intracranial pressure?

"Head pain due to a tumor is practically never acute and never tremendously severe. It is dull and often continuous. When it is localized and to one side or the other, it's a very reliable sign that the lesion is to that side. Another characteristic of head pain related to increased intracranial pressure or a brain tumor is that more often than not, if it's on the posterior fossa, it will be localized toward the back and if it is more anterior, toward the front. It is often accentuated in early morning on arising. The patient who says he wakes up with a dull, rather continuous headache may well have a brain tumor or increased pressure. Frequently this headache, although dull, is rather continuous and is exaggerated by a straining at the stool or by changes in position."

—ELI S. GOLDENSOHN, M.D., New York City  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# CASE REPORTS

## Foramen of Bochdalek Hernia With Acute Tension of Displaced Organs

NORMAN F. SEIDENVERG, M.D., *Vallejo*

HERNIATION THROUGH the pleural peritoneal canal which is located in the posterolateral region of the diaphragm is very uncommon in adults and I was unable to find in the literature a case presenting with acute tension of the herniated organs, as in the one here reported. In 1959, Kirkland<sup>1</sup> reviewed 34 previous cases of foramen of Bochdalek hernia and presented one more. In 1963 eight additional cases were reported, four by Sugg, Roper and Carlsson<sup>2</sup> and four by MacDougall, Abbott and Goodhand.<sup>3</sup> In 1966, Powers, Sejdinaj and Oberschneider<sup>4</sup> added one case for a total of 44 reported in the literature.

### Report of a Case

On December 9, 1968, a 20-year-old white woman was referred because an x-ray film taken in the family physician's office suggested complete pneumothorax on the left. Three days pre-

viously she had noted a slight pain in the left side of the chest while laughing, and shortly afterward she became nauseated and vomited. The pain then became less intense for a time and she rested well that evening. During the following two days, however, she was unable to eat and regurgitated and vomited all solids and most liquids.

Pain resumed intermittently, becoming more severe on December 8, with radiation to the left shoulder and along the left side of the chest. The patient said she had not had dyspnea but she did notice that she was breathing somewhat harder than usual. She had no history of trauma nor of any recent gastrointestinal problems. There was no previous history of medical abnormality of any kind.

Blood pressure at the time of admission to hospital was 140/88 mm of mercury, pulse 100 and regular, and temperature 37°C (98.6°F). The trachea, as palpated in the suprasternal notch, was shifted slightly to the right. Less than normal expansion of the left side of the chest was noted on inspiration, and resonance on percussion was greater on the left than the right. Breath sounds were normal on the right, diminished or absent on the left. Cardiac sounds were heard best to the right of the sternum and there was no murmur. No rales, wheezes or bowel sounds were present in the chest.

Hemoglobin was 13.2 grams per 100 ml of blood and leukocytes numbered 15,350 per cu mm with slight shift to the left. Urinalysis was within normal limits. An electrocardiogram showed no evidence of ischemia but did show positional deformity. Standard posterior-anterior and left lateral x-ray films of the chest showed a large sharply circumscribed collection of gas within the left

Submitted May 6, 1970.

Reprint requests to: 534 Oregon Street, Vallejo, Ca. 94590 (Dr. N. F. Seidenverg).



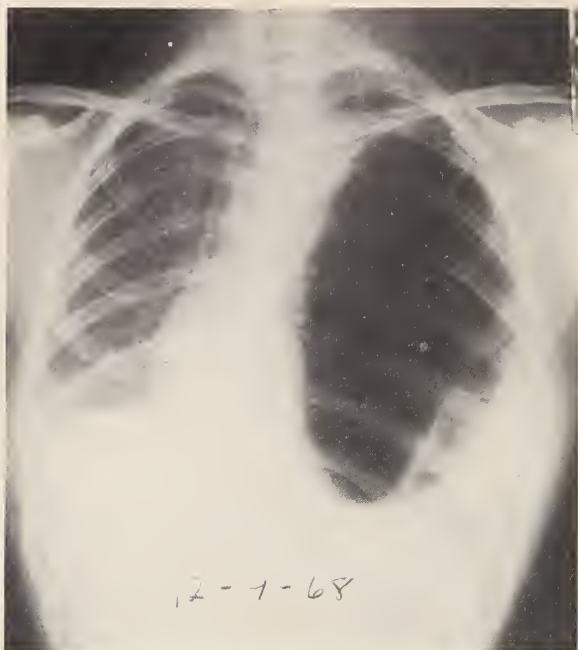


Figure 1.—A large sharply circumscribed collection of gas in left hemithorax, with mediastinum shifted to right and loops of bowel and fluid anteriorly and laterally in left side of chest.

thorax (Figure 1). The mediastinum was shifted to the right. No definite lung density was visible in the left hemithorax. A collection of gas was present in the left costophrenic angle with a small volume of fluid layered at the left costophrenic angle. The right lung was clear. The heart appeared normal in size but was shifted to the right. (An x-ray film of the chest taken by the referring physician in 1966 as a part of a routine physical examination showed no abnormality.)

With the patient in bed in a sitting position, a No. 18 needle with syringe and a three-way stopcock was inserted at the second left anterior intercostal space and 2000 cu ml of air was withdrawn. Following introduction of a nasogastric tube an x-ray film made at bedside showed the mediastinum returned to the midline, the left lung expanded superiorly and a gas-filled viscus (with nasogastric tube inside) filling about half of the left hemithorax (Figure 2).

Serial x-ray films showed gradual reduction in the size of the stomach which had herniated into the chest (Figure 3). Low intermittent suction was applied to the tube and intravenous maintenance was supplied overnight.

The next morning the abdomen was opened by upper midline incision and the entire stomach



Figure 2.—X-ray film taken after aspiration of air and introduction of nasogastric tube shows mediastinum returned to midline, left lung expanded superiorly and a gas-filled viscus (containing loop of tube) in left hemithorax.

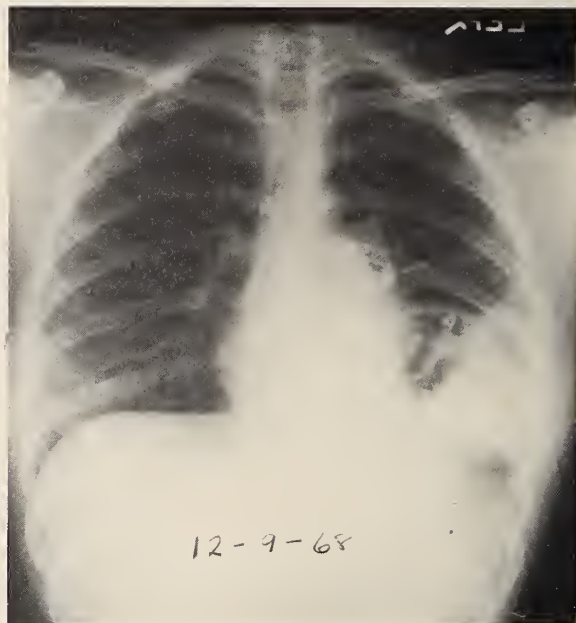


Figure 3.—Film taken evening before operation shows reduction (compared with Figure 2) in size of stomach herniated into chest.

(except for the distal pylorus), the spleen and the left side of the transverse colon were found to have herniated into the left side of the chest through a defect in the posterolateral aspect of the diaphragm. Thorough exploration of the abdomen showed no other abnormalities. The

colon was first reduced, then the gastrocolic omentum and part of the greater curvature of the stomach. The defect was found to be only 10 cm in horizontal and 6 cm in vertical diameter. Some difficulty was encountered in restoring the spleen to its normal place. The lung was easily reexpanded and the defect was closed with interrupted No. 1 silk sutures after a chest tube had been placed in the seventh left anterior intercostal space.

The patient did very well after operation and was discharged December 17 with all sutures and tubes removed. She was eating a regular diet and an x-ray film showed no abnormality (Figure 4). She remained well during 12 months of observation.

### Comments

None of the patients in the previously reported 44 cases presented with acute tension of the herniated organs in the chest. One of the cases reported by MacDougall, Abbott and Goodhand<sup>2</sup> was similar in that the stomach was massively dilated and aspiration was carried out through a needle placed in the left side of the chest. In that case, however, there was no tension and the presumable cause was trauma many years before, an upper gastrointestinal series having shown evidence of diaphragmatic hernia.

In the present case, atypical pneumothorax and acute dilatation of an abdominal viscus were considered in differential diagnosis. The left side of the chest was aspirated primarily to relieve the tension on the mediastinum and in the hope that serial x-ray studies would help clarify the diagnosis. The first film taken after aspiration of air was most helpful in suggesting that the cause was herniation of the stomach, and this was confirmed by roentgenographic visualization of the nasogastric tube in a viscus within the chest (Figure 2).

Use of an upper midline abdominal incision made exposure of the posterolateral defect in the diaphragm difficult but gave the advantage of a thorough abdominal exploration and avoidance of thoracotomy. The choice of a midline rather than a left paramedian or left subcostal incision was made because of preoperative impression of paraesophageal hernia; no consideration was given to the possibility of a defect in the pleural peritoneal canal.



Figure 4.—Postoperative x-ray film shows no abnormality of position or tension of organs.

### Summary

The first case of an acute foramen of Bochdalek hernia in an adult which presented with mediastinal shift due to acute gastric dilatation is discussed in detail.

Transabdominal reduction of the herniated organs and simple repair resulted in complete cure.

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# Mithramycin as a Possible Cause of Toxic Epidermal Necrolysis

(*Lyell's Syndrome*)

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TOXIC EPIDERMAL NECROLYSIS is a distinct syndrome, readily recognized by its sudden onset and the characteristic appearance of its lesions and readily confirmed by histological examination. At onset, erythema develops and spreads very rapidly over the body; the skin takes on a scalded appearance as if it had been burned. The sheets of "scalded" skin loosen and may be pushed about or pulled off the body. Histological study reveals a split in the epidermis just beneath the stratum corneum.

This syndrome has been reported sporadically under different names; current recognition by dermatologists dates from the description and renaming of the syndrome by Lyell in 1956.<sup>1</sup> The disease has etiologic characteristics of at least two orders: many cases, especially in children, seem to arise as a development of staphylococcal impetigo;<sup>2</sup> other cases, occurring equally in children and adults, suggest a drug reaction. The case reports presented here document a possible relationship of mithramycin to the development of Lyell's syndrome.

## Reports of Cases

*Case 1.* A 68-year-old man was admitted with a history of progressive personality changes, difficulties with balance and movement, and left hemiparesis following a syncopal episode two months earlier. Recent electroencephalograms had revealed a right frontotemporal focus and angiograms had shown a vascular mass in the region of the right frontal lobe. On admission the patient was somnolent and had episodes of crying when stimulated.

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Physical examination revealed bilateral papilledema and profound left hemiparesis. Intrinsic glioma was suspected, and large doses of dexamethasone (4 mg every 6 hours) were begun.

On the next day, a malignant glioma on the right frontal lobe was subtotally excised through a right frontal craniotomy. Immediate postoperative recovery was good, with no complications; left hemiparesis remained and the patient was mildly confused.

High-voltage irradiation was begun a week later for a total tumor dose of 3891 rads over 28 days. A 21-day regimen of intravenous mithramycin was begun a week after that. Toxic reaction to mithramycin, manifested by nausea and vomiting, necessitated some nasogastric feedings. Low serum sodium and a salt-losing syndrome developed and the patient became somewhat obtunded. Hemiparesis increased and sensorium decreased. Regular tube feedings were begun and the dosage of dexamethasone (which had been reduced gradually postoperatively) was increased, but there was little improvement in neurological status. A month after operation the patient became diaphoretic and a low-grade fever developed. Work-up revealed a urinary-tract infection which resolved to some extent when cephalothin (Keflin®) was administered.

Two days later, ulcers appeared inside the mouth and a diffuse rash appeared over the mouth and face. Sheets of skin in affected areas could be displaced readily by rubbing with a finger. The diagnosis of toxic epidermal necrolysis was made, and the rash was treated with iodochlorhydroxyquin (Vioform®) and triamcinolone acetonide cream. The patient became quite obtunded within three days and the rash spread down his chest to involve the upper extremities. His face, forehead and chest were denuded. Biopsy revealed a split in the epidermis beneath the stratum corneum. Mafenide hydrochloride (Sulfamylon®) cream was applied to the rash and intravenous fluid replacement was begun. The patient continued to grow worse and died 11 days after appearance of the rash.

The final diagnosis was: (1) malignant glioma, right frontal lobe, (2) toxic epidermal necrolysis (Lyell's syndrome), and (3) septicemia and pneumonitis.

*Case 2.* A 47-year-old woman was admitted to the Coronary Care Unit with complaint of palpitations and shortness of breath. Blood pressure

was 160/120 mm of mercury and the heart rate was 120. Rales were heard above lung bases. The patient improved with digitalis therapy. When clinical signs, lumbar puncture and angiograms suggested the presence of an intracranial mass, she was transferred to the Neurosurgical Service.

A left parietotemporal craniotomy was done and subtotal removal of a malignant glioma of the left angular gyrus was carried out. Postoperatively, the patient had profound right hemiparesis and aphasia, but no other complications. Three weeks after operation, a 21-day course of intravenous mithramycin was begun, and after five days of treatment with that drug, 1200 rads were delivered to the tumor site, with a planned tumor dose of 5000 rads to be administered over a six-week period. Nine days later aphasia and hemiparesis had progressed and the patient was fairly somnolent.

Dexamethasone (16 mg a day) was begun; she improved for four days and then status epilepticus developed. This was controlled with diazepam (Valium®). The platelet count was 33,000 per cu mm four days later. Frank gastrointestinal bleeding developed and the hematocrit fell to 27. Platelet packs and fresh blood were transfused over the next four days but the patient became more lethargic and profound right hemiparesis developed. A bilateral carotid arteriogram done two weeks later showed an avascular mass in the left hemisphere with pronounced shift of midline structures from left to right. Her family refused to allow further exploratory operation and her condition continued to deteriorate.

Two days after the arteriogram, ulcers developed in her mouth and an erythematous maculopapular rash appeared on her chest, arms and face. The skin was readily removed by gentle rubbing. Mafenide hydrochloride was applied to the rash. A diagnosis of toxic epidermal necrolysis (Lyell's syndrome) was made and confirmed by biopsy. The patient died two months after craniotomy.

Final diagnosis was: (1) astrocytoma, left angular gyrus, (2) toxic epidermal necrolysis (Lyell's syndrome), and (3) bilateral bronchopneumonia.

## Discussion

These patients clearly had toxic epidermal necrolysis, the sudden onset, widespread erythema, "scalded" appearance, denudation of skin and a

split in the epidermis beneath the stratum corneum being pathognomonic.

A bacterial cause was possible in these patients but not probable. Most cases of bacterial origin arise as an exaggeration of impetigo or of a skin disease that has undergone impetiginization (Phage type 71 staphylococci have been implicated as a common strain in this context), and neither of these patients had a history of skin eruptions of any type. Attempts to demonstrate organisms in the blisters might have been helpful in establishing the cause.

The problems of determining that a drug was an etiologic factor in a cutaneous eruption are exemplified here. First, even though mithramycin was administered to both patients, so were other drugs, and the relationship would have been more straightforward had no other drugs been used. Second, drug challenge with successful reproduction of lesions, which is the most definitive way to determine that a drug was the cause, was not possible in either of these patients. Whether the dexamethasone given to these patients before the appearance of their rash mitigated the severity of their toxic epidermal necrolysis remains speculative.

The possibility exists, of course, that the syndrome in these patients was caused by neither a bacteria nor a drug. At present, this again remains speculative, and is less probable than that mithramycin caused the disease.

## Summary

Toxic epidermal necrolysis (Lyell's syndrome) developed in two patients as a terminal event. Both patients had undergone operative removal of malignant gliomas, both were completing a 21-day course of intravenous mithramycin as well as supravoltage irradiation of the tumor bed, and both were receiving large doses of dexamethasone and antibiotics. While a bacterial cause of this disorder cannot be ruled out, a drug-related cause (in this case, mithramycin) is more probable.

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# Ancient Stench and Present-Day Effluent

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A SAMENESS IN OUR DAILY LIVES is something we accept without thinking. For any large-city dweller, smog is a part of this sameness, as are chlorinated water and newspaper articles on pollution. He *looks* at these things but does not *see* them.

People have adapted to air pollution, but, as René Dubos has indicated, they have overlooked its later subtler complications. These may appear as chronic respiratory disease, and possibly cancer and vascular disease.<sup>1</sup> A possibility of remote effects of pollution was raised by the phenomenon that in a series of male patients who died of Hodgkin's disease a large number had had some exposure to wood in the course of their work. This suggested the presence in wood, trees or bark of a substance having the ability to cause Hodgkin's disease.<sup>2</sup> Although there is no definite evidence that this substance might be a pesticide used in forests, the possibility is worth considering.

Communities have even disregarded instances of obvious and immediate pollution. A black fog descended on London in December, 1952. During four days of almost no visibility, accidents, illness and crime produced 4000 deaths over the normal.<sup>3</sup> Londoners scarcely realized the dangers during this period, and soon forgot about the episode.

An increasing population compounds the problem of pollution. By 1850, after a very gradual increase over many centuries, the total popula-

tion of the world reached one billion. In 1925, it was two billion; by 1960, three billion. Demographers expect it to reach four billion by 1975.<sup>4</sup> The two percent increase will contribute its share of pollution. As recently as 1959, however, a standard text on public health had little reference to birth control.<sup>5</sup> It was not until 1966 that any significant federal effort went into family planning.<sup>4</sup> A recent scanning of federal programs revealed spending as follows (1969 estimates from the 1970 budget):<sup>6</sup>

Federal Health Programs	\$ 11 billion
Space Program	4 billion
Grants to States for Welfare	3.4 billion
Food for Peace Exports	900 million
Crime control	639 million
Supersonic aircraft	126 million
Air pollution	85 million
Population control (U.S.)	65 million
Population control (foreign)	51 million

Affluence, based on expanding industrial production, contributes to many of our pollution problems, and wealthy communities, in turn, *buy* their way out of these problems. The United States has spent much on automobile anti-smog devices and large-scale water purification projects. Considerable discussion centers on pollution control, but the wheels move slowly. The Secretary of Health, Education, and Welfare announced recently a "two-year phase-out of DDT."<sup>7</sup> There are limits to spending, however, and to general measures involving huge majorities. Industry could free Lake Erie from most of its present foul state by closing the 300 plants

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lining its shores. Motorists could eliminate most city smog by throwing away the keys to their automobiles. Such sacrifices, however, are not in keeping with our present economic sprint.

Individual action usually occurs only when problems of pollution affect one visibly or personally. The woodworker with Hodgkin's disease and the mineworker with silicosis and tuberculosis may be individual victims of pollution, though for them the awareness may come too late. The man in a new subdivision who suddenly finds that his home is adjacent to a piggery, has a constant odor to provoke him to action. But individual feeling can likewise play a role in resisting objective pollution control measures. Smokers reacted antagonistically toward a recommendation made by an American Cancer Society official that smoking be prohibited indoors or in confined areas.

In antiquity, pollution usually affected an individual directly. Fear stimulated response, especially to defilement of unknown cause. Fear of death from disease resulted in such concepts as *mal aria* (bad air), an atmosphere which contained disease. Akin to this was the concept of pollution by evil spirits, supernatural causes, and curses, with remedies consisting of prayers, exorcism and incantation. The savage often placed holy and polluted persons in the same category; both were dangerous, and the underlying basis was ghostly and imaginary. Taboos evolved for protection against these spiritual dangers.<sup>8</sup> For the ancient Hawaiian, fear promoted anti-pollution measures in two ways: he carefully buried his personal waste, even nail parings and hair, so that a sorcerer would not pray over it to put a spell on him; and he avoided casting this waste into water sources or the sea because water was the gift of an ancestral god whose dwelling place was sacrosanct.<sup>9</sup>

The word *pollute* comes from the Latin *polluere*; it means, according to Webster, "to make or render unclean; to defile; desecrate; profane." The concept long antedated the Romans, however. Related words, also with a long history, include be foul, tarnish, taint and corrupt.

For the ancient Egyptian, whose very life depended on the yearly rising of the Nile, water pollution provided a constant problem. Strict laws forbade contaminating the river waters with human waste, and punishments were harsh.

Pollution in Egypt usually involved putrefac-

tion. The stimulus to explain this latter phenomenon was an itch in the minds of men for many centuries until Pasteur evolved the germ theory of disease a hundred years ago.<sup>10</sup> Knowledge of specific bacteria alleviated much of the fear connected with the cause of communicable disease.

The Egyptians described a foul principle, *whdw*, adherent to feces, as the cause of putrefaction, decay and fermentation.<sup>11</sup> Herodotus records that they believed it was a residual of food eaten, that it caused disease, and that they used emetics and clysters as purges for three days each month to rid themselves of it.<sup>12</sup> They believed the *whdw* resulted also in purulence which lodged in swellings and abscesses. In the Hearst Papyrus, Prescriptions 140 and 141 were designed "to bring forth pus," and contained frankincense and an alkaline astringent.<sup>11</sup>

The concept of *whdw* extended to the putrefaction of corpses, and stimulated the preservation and mummification of dead bodies, crafts in which the Egyptians became very proficient. The god who commanded reverence from both physician and embalmer was one and the same, Anubis.<sup>13</sup>

The idea of the putrefaction of all organic matter came directly from Egyptian medicine to Greek medicine.<sup>13</sup> The Greeks believed that rotting termed *pepsis* took place in the upper part of the body, while that called *sepsis* occurred in the lower part. They emphasized ridding the body of any surfeit (residue of ingested food) which might become putrefied. The Hippocratic writing, *On Regimen*, mentions surfeit's giving rise to constipation and fever.<sup>14</sup> Emetics and purging formed a prominent part of Greek therapy. Even today some people use castor oil as early treatment for fever or an upper respiratory infection.

The Greeks believed that products of putrefaction spread throughout the body to cause foci of disease. A modern counterpart of this idea is the concept of focal infection stemming from a putrefactive source, and the removal of carious teeth or infected tonsils as suspected sources. The Greeks placed fresh meat on a painful swelling as a poultice, and visualized the essence of putrefaction passing into the meat. This "fossil" persists today in the use of a piece of beefsteak for a black eye. They believed the essence also entered blood vessels of the bowel and cir-



culated. A means to liberate this was blood-letting, a practice used by countless physicians for centuries, and still extant today. Galen's concepts included that of *cacochymia*, putrefaction of the chyme; he also advised venesection for fever.<sup>15</sup>

Putrefaction results in heat and odor, and it was Praxagoras who noted that a foul odor from decaying meat could reside for hours in clothing. At the same time, meat lost weight as it putrefied. This stimulated the idea that minute separate particles (*particulate matter*), containing odor, arise from decaying organic matter. Democritus (460-360 BC) spoke of particulate matter in a theory that life results from "a fortuitous concourse of atoms."<sup>16</sup> He denied Hippocrates' "unity of the organism," and he later concerned himself with the cause of epidemic diseases.

Lucretius (95-55 BC) expanded the ideas on particulate matter in his poem, *De Rerum Natura*:

For since they wander through the void  
inane,  
All the primordial germs of things must  
needs

Be borne along, either by weight their own,  
Or haply by another's blow without.

.....  
No rest is rendered to the primal bodies  
Along the unfathomable inane; but rather  
Inveterately plied by motions mixed,  
Some, at their jamming, bound aback and  
leave

Huge gaps between, and some from off the  
blow

Are hurried about with spaces small be-  
tween.

And all which, brought together with slight  
gaps,

In more condensed union bound aback,  
Linked by their own all inter-tangled  
shapes,—

These form the irrefragable roots of rocks  
And the brute bulks of iron, and what else  
Is of their kind .....<sup>17</sup>

He writes of odor, *De Odore*, in relation to minute particles:

To speak once more of odour;  
Whatever assails the nostrils, some can travel  
A longer way than others. None of them,  
However, 's borne so far as sound or voice—  
While I omit all mention of such things  
As hit the eyesight and assail the vision.

For slowly on a wandering course it comes  
And perishes sooner, by degrees absorbed  
Easily into all the winds of air;—

.....  
Thou mayest see that odour is create  
Of larger primal germs than voice, because  
It enters not through stony walls, where-  
through

Unfailingly the voice and sound are borne;  
Whereof, besides, thou wilt observe 'tis not  
So easy to trace out in whatso place  
The smelling object is. For dallying on  
Along the winds, the particles cool off,  
And then the scurrying messengers of things  
Arrive our senses, when no longer hot.  
So dogs oft wander astray, and hunt the  
scent.<sup>18</sup>

One remembers Fracastoro (1478-1553) best for his poem on syphilis. In his *De contagione et contagiosis morbis* (1546), however, he contributed to the theory of particulate matter. He described three types of contagion: (1) by direct contact, (2) by indirect contact, through particles of infection, *seminaria prima*, carried by secondary articles such as clothes, and (3) by distant transmission.<sup>19</sup> In explaining indirect contact, he writes:

Do we not observe that in wood, clothes, etc., a strange smell may be preserved for a long time, and that not due to some definite quality in them without material basis, but rather to bodies so very small as to be invisible to us?<sup>20</sup>

John Hunter contributed to our knowledge of the reception of odors when he dissected out the branches of the olfactory nerve in the nose.<sup>21</sup> The final evolvement of the true molecular theory, and the recognition of the effect of molecules of certain shapes and sizes on special receptors in the olfactory apparatus, according to a stereological pattern, has rounded out our comprehension of this subject.

Olfactory sensation has always provided a means of detecting areas of pollution or disease. Strong foul odors such as those of indole, skatole, and ammonia, from human wastes, and putrescine and cadaverine from corpses, cause immediate revulsion to polluted material or areas. In one recent year American housewives spent 60 million dollars on scented aerosol preparations to counteract unpleasant household odors.<sup>22</sup> Were foul odors associated with all forms of pol-

lution today, public action might be accelerated and more effective.

Early people stigmatized the miasma (*malaria*) of swamps, a noxious effluvium often floating on night mists, as the cause of malaria. The Hippocratic writing, *Airs, Waters, and Places*, notes that:

Such waters then as are marshy, stagnant, and belong to lakes, are necessarily hot in summer, thick, and have a strong smell, since they have no current . . . . . Those who drink them have large and obstructed spleens . . . . . and in summer dysenteries, diarrhoeas, and protracted quartan fevers frequently seize them . . . . .<sup>23</sup>

This idea of miasma causing malaria persisted until a generation ago when, after the work of Laveran, Manson and Ross, Louis Sambon proved he could live in the marshes of Lagos, Nigeria, without getting malaria, simply by sleeping under netting at night.

Early measures to counteract evil odors or evils consisted in the use of other odors, often evil-smelling themselves. The anti-demoniacal pharmacology of the Assyrians contained asafoetida, usually used for hysteria, and present-day pharmacology texts still list it.<sup>24</sup> The burning of sulfur to cleanse a room, the burning of green sticks to liberate formaldehyde, the use of incense and joss-sticks, and Lister's phenol spray are all examples of smells that counteract bad smells or pollution. Tobacco smoke was used in the form of enemas from the Seventeenth to Nineteenth Centuries for various conditions such as constipation and colic, and even for drowned persons.<sup>25</sup> According to one report, the writings of the Indian physician, Charaka, probably from about the time of Christ, describe fumigation and sterilization by steam.<sup>26</sup>

In the history of Israel also, pollution was often an individual affair. Observations of personal contamination probably reflected, in part, a relationship to hygiene and disease, and resulted in early Mosaic regulation:

If anyone touches an unclean thing, whether the carcass of an unclean beast or a carcass of unclean cattle or a carcass of unclean swarming things, and it is hidden from him, and he has become unclean, he shall be guilty.<sup>27</sup>

The passage and it is hidden from him refers to

a lack of knowledge of becoming unclean on the part of an individual, but one might interpret here also a respect for a hidden transmission of disease.

Old Testament writings regarding pollution specified very clearly restrictions and purifications in regard to the eating of the meat of certain animals, fish, birds and insects, and with regard to personal hygiene, menstruation, childbirth, sexual relations, circumcision, leprosy and ulcerations with discharges.<sup>28</sup> They based restrictions probably both on health and a moral regard for all living things.

Mosaic concepts associated the shedding of blood with pollution:

They poured out innocent blood,  
the blood of their sons and daughters  
whom they sacrificed to the idols of Canaan,  
and the land was polluted with blood.  
Thus they became unclean by their acts.<sup>29</sup>

In the Mosaic Age, as in most ancient times, any wound which shed blood became infected, and acquired the putrefactive and odorous qualities associated with pollution. High morbidity in wounds and a high mortality in infections perhaps evolved a religious stigma or taboo on such acts associated with bloodshed.

Intimate contact with a dying man resulted in defilement. Executioners resorted to stoning from a distance rather than killing at close quarters in order to avoid contamination.<sup>30</sup> A description from Plato tells of pollution of a town resulting from a man murdering one of his own family. Purification took the form of stoning the executed man's body by magistrates outside the walls of the town.<sup>31</sup>

The New Testament also exemplifies ancient concepts of pollution in association with dead bodies:

Woe to you, scribes and Pharisees, hypocrites! for you are like whitewashed tombs, which outwardly appear beautiful, but within they are full of dead men's bones and all uncleanness.<sup>32</sup>

In other cultures, contact with the dead resulted in defilement also. Mourners in Japan immersed themselves in water after contact with the dead.<sup>33</sup> At Hierapolis-Bambyce, if one of the sacred eunuchs saw the corpse of one of his relations, the people declared that he was unclean for thirty days. Before he could again set



foot within the holy preeinct, his head was shaved.<sup>34</sup>

Christian concepts of purification of polluted spirits appear in the New Testament:

And he called to him his twelve disciples and gave them authority over unclean spirits, to cast them out, and to heal every disease and every infirmity.<sup>35</sup>

The period for isolation of polluted persons may have had some relationship to suspected incubation periods. Forty days eventually evolved as the time of segregation for smallpox—hence the term *quarantine*, from the Italian word for forty.

Defilement was likewise a state of mind:

I know and am persuaded in the Lord Jesus that nothing is unclean in itself; but it is unclean for any one who thinks it is unclean.<sup>36</sup>

An idea that Desdemona was unfaithful polluted Othello's mind, a handkerchief being the suspected evidence. Reaction to this taint resulted in his taking her life.<sup>37</sup>

Deliberate and immediate pollution usually causes conspicuous reaction. In April, 1915, during World War I, the Germans introduced poison gas by using chlorine at Ypres. Later, casualties among American soldiers were as high as 30 percent from this form of warfare. The strong revulsion against poison gas prevented its use in World War II. Such revulsion seems to be present so far in regard to bacteriological warfare.

Our present age, with all of our technical development, should be less cluttered than it is. Yet our social problems, on close scrutiny, are almost as great as the plagues of antiquity, though perhaps the effects are more obscure. To develop the concern that is necessary to contain the expanding problems of pollution, present-day communities need the individual involvement, odors, and fear that prompted the vigorous reactions to pollution in ancient times.

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## A Timely Correspondence

EDITOR'S NOTE: *The following letters between Ray Lyman Wilbur, M.D., then Chancellor of Stanford University, and Earl Warren, then Governor of the State of California, were felt by Dwight L. Wilbur, M.D., once again to be timely and he has suggested that they might now be published in CALIFORNIA MEDICINE. We agree.*

February 9, 1945.

Governor Earl Warren,  
State Capitol,  
Sacramento, California.

My dear Governor Warren:

It was a privilege to attend that meeting at the Family Club and discuss prepaid medical care. I am deeply concerned with the turn taken in public discussions of and the proposals for new schemes of providing medical service for the people of California. Before the discussions get out of hand and turn into bitter controversies that make harder going for everyone, I should like to present to you some of the factors that seem significant at this time.

As I understand it, we want, *in operation*, a plan that will provide for the people of California adequate, scientific medical service at a cost which can be reasonably met by all, whatever their respective stations in life. This would mean attainment of a major social objective, to which there are no single nor simple answers. Social progress does not happen that way except on Utopian blueprints; but we can be proud of some real accomplishments in this state. As a physician, as a public official, and as a private citizen concerned about the welfare of the people around me, I have been trying for some years to understand and do something about this complex problem.

It seems to me that we now have an unparal-

leled opportunity for forward progress here in California, if we consider carefully the next steps that are to be taken.

Copies of the several bills designed to extend the provision of medical care have not yet reached me, but from what I have heard of the three most frequently mentioned none builds on existing foundations nor takes fully into account the several functioning plans that provide a practical, usable backlog of experience.

Various organizations, such as the University of California, the Southern Pacific Company, the Pacific Gas & Electric Company, Standard Oil, the Bell Telephone Company, and lately the Kaiser organizations, have offered for students and employees plans of medical service and hospital care of varying degrees of completeness. Municipalities have been endeavoring to meet the problems of employees and their families in different ways: Los Angeles, working in cooperation with the Ross-Loos Clinic; San Francisco with its plan for county employees. We have a considerable investment in public and private general hospitals and special hospitals and an important structure of public health extending from the state through counties and cities.

Most significant of all of the plans in the State is the California Physicians' Service, as it is sponsored by the doctors themselves. In it a majority of our California physicians and surgeons have assumed a responsibility in a manner that is unique.

It would seem wise to utilize these beginnings and build on the start that has been made. Small though it is now, the California Physicians' Service is an important "pilot plan." As such, it deserves extension and further testing. The present 100,000 membership ought to be increased



to a million and more. Backed with funds and moral encouragement this organization could be utilized to make an outstanding demonstration of public and private cooperation.

I believe that it is possible to formulate permissive legislation which will not in effect junk the sound beginnings that have been made. It can be peculiarly Western in its form, rather than cut on any New Deal or European compulsory pattern; and it can put California in the lead in showing that the medical care problem can be dealt with on a *quality* service basis.

The red herring of "doctor's monopoly" will be dragged out, but the fallacy of this is easy to answer. In connection with medical practice the only element of monopoly is the State's own requirement of an examination for a license to practice medicine and surgery. This is a safeguard against malpractice and inadequate educational preparation. In the CPS program every physician must be able to obtain malpractice insurance and meet the State requirements in education. I believe that this is important in order to keep the great traditions and ideals of the medical profession at work instead of distorting them into obstacles to progress. We need evolution of the best, rather than revolution. I hope that one of the outstanding achievements of your administration will be a program of health which will set an example for other states.

I regret that the "bump" I had last year makes it impossible for me to take on a full working program, but if I can be helpful in an advisory way I would be glad to have you call on me.

Faithfully,

RAY LYMAN WILBUR

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STANFORD UNIVERSITY

Office of the Chancellor

March 22, 1945.

My dear Governor Warren:

Following our conversation over the telephone a few days ago I have been reviewing the whole subject of prepaid medical care to see whether we could get out of the present legislative snarl which seems to be developing more heat than light. I am still hopeful that some positive accomplishments may come about at this session of the legislature.

As you realize, this is one of the most difficult of social and governmental problems, since everyone is involved to some degree. I am more than ever convinced that compulsion of the physician and of the family is not the answer. This compulsion will be applied to too many unwilling people to have it work well. We have made too many important gains in the United States, and particularly in California, on a voluntary basis to substitute for them expensive theoretically-planned schemes, no matter how beneficent they may seem.

You may feel that I am anchored in the past and unwilling to go along with change; but the fact is that there has been no change in the fundamentals of science applied to the care of the sick and the prevention of disease. These fundamentals depend upon research, experience, and long and expert training. We must have experts in this field who can be abreast of the advances of science and who know their business. They can be understood only by those who know the possibilities of modern medicine. No political group or board, no vested interest, no governmental unit, no matter how large or how well financed, can be trusted to make wise, lasting and forward-looking decisions in this human activity which requires the tests and the judgment of the experts. Social theories that will push us backward, rather than forward, in the fight for better health are always a menace. I have worked too long and too intensively for improving the standards of medical education and medical care to be complacent about seeing them dumped on the scrap heap. Arguments that are advanced about what has happened in Russia, England, or Germany, or Holland fall short of the mark. I have seen something of all of these except those of Russia. Not one of those countries has ever attained for like numbers of people the quality or quantity of medical care that we take for granted. Their public health organizations function differently. Their standards of what constitutes adequate medical care do not measure up to ours.

I have a firm faith that the voluntary method has worked better in this country than any compulsory scheme could possibly have done. I believe that it will work better in the future if we put more steam behind it. As I indicated in my previous letter to you, under date of February 9th, we have a number of voluntary plans. All

of them are based on somewhat limited service, but service of excellent quality. In the California Physicians' Service our State has a unique and significant voluntary plan with which to work, a plan that has struggled through the vicissitudes of youth and has gained experience. Admittedly, the California Physicians' Service is not perfect and has not always functioned as smoothly as we should like, but through experimentation, through trial and error, we have learned more about practical working procedures under American conditions than has any other such non-profit organization. Certainly it would seem wiser to foster the development of such an organization, to utilize its experience and to help in the extension of its usefulness, than to discard it and other voluntary procedures for a heavily financed theoretical setup that has never been tested and that has never worked adequately anywhere. When several thousand forward-looking physicians of the State have accepted responsibility for a social experiment as important as this, it should not be destroyed and the experience gained by it discarded.

May I ask for a reconsideration of this whole problem to see whether you will not discover that it would be wiser to help the physicians carry on the difficult and complicated task for which they alone can provide the expert physicians and surgeons. This is not a question of economics alone. It is not 3% of so many pay-rolls divided among so many doctors. It involves quality in medical care, in medical education which is expensive, and in medical research. It must include hospitals, clinics, laboratories, and all of the appurtenances of modern medical practice and the personnel required for them.

I was much pleased when you took hold of this subject, since it happens that I have been working on this difficult problem for a long time and with many people who have been seeking a solution. I should like to see California in the vanguard. I believe that we can make a demonstration through the California Physicians' Service that will be valuable to every other state in the Union. I think that there is no need to destroy any existing medical center of quality or any other voluntary procedure by which a group of physicians, trained in accordance with the laws of the State, can organize to take care of groups of citizens who need their care on a prepaid basis with voluntary choices of physi-

cians and hospitals. There is no substitute in the protection of the people for high quality of preparation and training. The doctor is an individual. Each patient is an individual. No two individuals are born alike or trained alike, and any nickel in the slot or capitation method of medical care is bound to be costly, controlled by ignorance, and full of peril.

The California Physicians' Service is planning to have a meeting in Sacramento on April 7th. If there are any questions which you would like to discuss with us at that time I would be glad to arrange to save some time for you on our agenda. I am sending a copy of this letter to our CPS Board of Directors.

Very sincerely,

RAY LYMAN WILBUR

Governor Earl Warren,  
Sacramento, California.

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#### STATE OF CALIFORNIA

Earl Warren  
Governor

GOVERNOR'S OFFICE  
Sacramento

April 3, 1945.

The Honorable Ray Lyman Wilbur  
Chancellor, Stanford University  
Palo Alto, California.

My dear Doctor:

I received your letter of March 22nd concerning the health insurance bill, but unfortunately only after it had been released to the press by the California Medical Association's publicity agent as propaganda against the bill. I was therefore compelled by circumstances—but I assure you, against my desires—to discuss it with the press.

This whole situation has developed an attitude of bitterness on the part of many doctors that is incomprehensible to me. The health bill has been referred to as State Medicine, Socialized Medicine, an alien philosophy born in Germany, and numerous other epithets that come with bad grace from the California Medical Association, which sponsored a similar bill in our State Legislature only ten years ago.



Before causing this legislation to be introduced, I consulted with the doctors, as you know, and was encouraged to believe that they recognized that a serious problem existed and that they believed that all of us having responsibilities in the field of public health should play a part in solving it. However, immediately after the meeting of the House of Delegates in Los Angeles, the attitude changed from cooperation to bitterness.

In spite of all this, I have tried to keep the discussion on a high plane, claiming no particular knowledge on the subject myself but asking only for cooperation in trying to meet the situation. I have no pride of authorship in the bill which we presented to the Legislature, and I have no doubt that improvements can be made in it. At all times I have been willing to make a modest beginning, if necessary, as a foundation for future development. However, to my great disappointment, I have never received from the Medical Association a suggestion or an alternative that would be helpful in the situation. Its campaign has been negative in every respect and has been typified by the speeches of Dr. Goin who stated, according to the press, that 95% of the doctors, including himself, would not cooperate in such a program even if the State should adopt such a program. He also stated on that occasion that he had never heard of any lack of medical care under our present system and that if there was any such lack of care it was caused by "superstition, religion, fear or procrastination."

I know of your great interest in this field and the contributions you have made throughout the years. I had hoped that you would be one of my allies in this fight. I was more firmly of that opinion after my conference with the Executive Committee of the California Medical Association, at which both you and I expressed ourselves on the subject. I sincerely regret that I have not had the opportunity to talk to you more often, as I am sure our innermost convictions are not so far apart as your last letter would indicate. Your offer to allow me to speak before the representatives of the California Physicians' Service is appreciated, but I believe no particular good would come from such an appearance. They are apparently too strongly committed against any legislative change. However, I want you to know that I have the highest regard for

these gentlemen and would do anything in my power to assist them. You know, of course, that I am always happy to talk to you on this or any other subject. I have delayed answering your letter for some days because I did not desire to discuss my answer with the press.

Hoping to see you when you are in Sacramento, and with best wishes, I am

Sincerely,

EARL WARREN  
*Governor*

April 11, 1945.

Dear Governor Warren:

Thank you for your gracious letter of April 3rd, which reached me while I was taking a little rest period on a ranch in the lower San Joaquin.

It is to be regretted that the legislature has not faced the so-called health insurance issue. I am not proud of certain features of the campaign made against legislative action at this time. When I learned that there was to be a meeting of the Directors of the California Physicians' Service in Sacramento I wanted to have the courtesy of an invitation extended to you, just as you had invited members of the medical society to that meeting at the Family Club. Since this required Board action I sent to the members of the Board a confidential copy of my letter to you of March 22nd. This confidential copy was used rather freely without my consent. Apparently in the heat of controversy the essentials that I had in mind of a group of qualified physicians and surgeons providing prepaid medical care to a group of voluntary patients was by-passed.

Nevertheless I think that a great deal of good was gained by the discussion, since in a complicated social problem of this sort the more discussion the better. All the way through we have found it a most difficult subject to discuss because of the tendency to make charges rather than to seek for typical and workable plans. I think that this is a field in which there will be continued discussion and in which your leadership will continue to be helpful in getting an adequate solution.

With kindest personal wishes,

Faithfully,

RAY LYMAN WILBUR

Governor Earl Warren,  
Sacramento, California.

# LETTERS *to the Editor*

## Further Words About DDT

*To the Editor:* There are many environmental problems that may affect health adversely. Accordingly, it is unfortunate that the cover of CALIFORNIA MEDICINE for November, 1970, and the article by Edgar Wayburn, "Man, Medicine and Ecology—An Overview," should have selected DDT as a main target, since DDT has been the greatest aid to medicine of any chemical in history.

Dr. Wayburn specifically selects for one of his criticisms the use of DDT in spraying walls to control malaria as a mosquito adulticide. The program based on this procedure was estimated to have saved 5 million lives and prevented 100 million illnesses in the first eight years of its use. The WHO commented that "no symptoms have been observed among the spraymen or among the inhabitants of the spray areas," numbering 130,000 and 535 million at the peak of the campaign.<sup>1</sup> Dr. Wayburn regales us with the latest version of the cat-rat story which I believe first appeared in 1962 as a Vietnam anecdote in the New York Times. The current "Sarawak variation" received the following comment by the WHO in 1969: "DDT as applied has not caused any side effects among domestic animals (the matter of the North Borneo cats as misinterpreted in TIME concerned Dieldrin, not DDT)."<sup>1</sup> It would be interesting to learn whether the cats died of, let's say, feline viral panleucopenia, and whether cats actually eat cockroaches.<sup>2</sup>

A further credibility gap is imposed by the fact that DDT is one of the least toxic of any of the pesticides to warm-blooded animals.<sup>3</sup> The LD<sub>50</sub> of DDT for cats is about 300 mg per kilo of body weight.<sup>4,1a</sup> DDT has an LD<sub>50</sub> of 25 micrograms per insect for DDT-resistant cockroaches.<sup>5</sup>

A 5-kilo cat would have to eat 60,000 cockroaches in one day to ingest a lethal dose of DDT, assuming that the cockroaches had received an LD<sub>50</sub> sufficient to kill 50 percent of the cockroaches in a resistant population. Under such circumstances, the death of the cat might be due to (a) ruptured intestines from impaction by the cockroaches (b) physical exhaustion—the cat would have to catch 42 cockroaches per minute for 24 hours. There remains the question of the wall geckos. Since these animals are poikilothermic, they are probably more susceptible to DDT than are mammals. This would pose a problem for the cats in having to eat more than their own weight of geckos to obtain a lethal dose of DDT. However, the cats would probably be too busy chasing cockroaches to catch many geckos. The cat-cockroach relationship has been discussed by Marquis.<sup>2</sup>

Dr. Wayburn also states that "DDT is now present in human mother's milk in concentration considered illegal for animal milk by the U.S. Food and Drug Administration." This is an incomplete story. The DDT tolerance in cow's milk was set at less than one one-hundredth of the tolerance for other foods. This latter tolerance was set at one one-hundredth of the estimated LD<sub>50</sub>, so DDT has a legal tolerance in milk of less than one ten-thousandth of the estimated toxic level. I know of no other substance, even water, that would pass such a requirement. Wayland Hayes, M.D., commented on June 4, 1970: "There is nothing new about the presence of DDT in human milk; it is just the relationship of its concentrations in human and cow's milk that was noted in 1965 and completely misinterpreted recently by persons without training in medicine."<sup>6</sup> Dr. Hayes was chairman of the meeting that set the "permissible rate" for DDT intake by breast-



fed infants. He also comments that preweanling rats are more than twice as resistant as adults to DDT, and newborn rats are more than 20 times as resistant as adults, and that the safety factor of the WHO "permissible rate" for infants is 150 times the dosage of DDT which was given daily for six months to a patient with jaundice.

An appraisal of DDT was made by the Committee on Occupational Toxicology of the A.M.A. (J.Amer.Med.Assoc., 212, 1055, 1970). The authors recommend continuation of the use of DDT under suitable precautions, and they state that careful research has shown no interference, despite long-continued exposure, with the health of pesticide handlers with concentrations of DDT in the fat as much as 50 times as high as in the general population.

No one should question the importance of studying and controlling pollution. For example, the dumping of mercury into lakes and streams is quite indefensible, and is an obvious hazard to health. In contrast, the proper use of DDT has been of great benefit in the control of disease, and evidence for harmful effects of DDT on human beings is lacking.

THOMAS H. JUKES, PH.D.  
Professor of Medical Physics  
University of California, Berkeley

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*To the Editor:* Because of the way in which Ecology has suddenly been brought to public attention, the public and no doubt even many physicians are left unaware of the fact that for years there have been a substantial number of professional ecologists working with limited support and yet with considerable success to improve our environment for the benefit of *human beings*. (I emphasize human beings because those "ecolo-

gists" who have received most attention from the mass media seem to be primarily concerned with the health of rare birds and fishes.) Specifically, I refer to public health workers, foresters, and agricultural workers.

As a one-time public health worker, I know a good deal about the lack of support that has handicapped most workers in these fields whenever they have found themselves trying to enforce a health or conservation law which came into conflict with some politically well-connected real estate developer, oil driller or manufacturer. When that has happened, very often the public official has either been overridden by his political bosses or, if he was too resolute, has simply been fired or replaced by someone with more "understanding."

Now, to add to the problems that public health, conservation and agricultural workers have to face is the public confusion that has been created by the anti-DDT campaign set off by an assistant professor of chemistry—Charles Wurster—and a lawyer, Victor Yannecone.

The basic ecological facts about DDT are these:

1. It is the main cause of the population explosion in the three southern continents where malaria and other insect-borne diseases have been (and still are) the major causes of disability and death. There are no doubt hundreds of millions of people living today, and living in a state of health, who were it not for DDT would be living with chronic malaria or be dead.

2. Furthermore, were it not for the great increases in agricultural production that have resulted from the use of DDT, many of these people would have starved to death.

3. And this is the clincher. Though millions and millions of pounds of DDT have been manufactured by hundreds of chemical plant workers and sprayed by thousands of public health workers, not *one single death* has ever occurred in these workers. Of course they have been exposed to DDT in quantities many times that of the average person. And those who have worked for as long as 25 years in the Montrose DDT manufacturing plant have been examined periodically by the USPHS. If anything, they have enjoyed better than average health and have produced a substantial number of healthy offspring. There is *no other chemical in use to protect human health* with a record that comes close to this. To pin that down, I remind you that there are more than 200 deaths per year attributed to aspirin.

4. In the face of this safety and efficacy record, I am puzzled every time I read that the search is on to find a safer insecticide than DDT. How much safer than 100 percent can an insecticide be? Regarding the concern about brown pelicans, peregrine falcons, bald eagles and so on, I refer you to Professor Gordon Edwards of San Jose, who has thoroughly refuted these claims.<sup>1</sup>

5. The claim by Wurster that DDT can break the marine biological chain by destroying the reproductive and oxygen-releasing capacity of phytoplankton has been completely refuted in *SCIENCE* by Machta and Hughes<sup>2</sup> and by Broecker.<sup>3</sup>

The most unfortunate aspects of the anti-DDT campaign are these:

A. Though there are many serious air, water and land pollution problems to be combatted, the anti-DDT campaign has had the effect of converting the Audubon Society, the Sierra Club and the news media into opponents rather than supporters of the professional public health, forestry and agricultural workers mentioned above. Many of these workers have been forced to spend a great deal of time and energy over the past two or three years trying to counter the mindless campaign that has been carried on. You may ask why they worked so hard to defend DDT. The answer is that if you can't justify the use of DDT, you can't justify any other insecticide, for not one of them is as safe or as effective or as cheap to use as DDT.

B. As a result of this factually distorted and hysterical campaign against DDT, a major credibility gap has been created which will take years to overcome. How the news media, certain politicians and Professor Wurster will ever explain their gross exaggerations and fear-mongering to the public will be interesting to watch.

It is most unfortunate that Dr. Wayburn's article "Man, Medicine and Ecology" (November 1970, pages 1-6)—which in its over-all intent I approve—should add more fuel to the anti-DDT campaign at the very time when the truth is slowly beginning to emerge.

JOSEPH W. STILL, M.D., M.P.H.  
Los Angeles

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*To the Editor:* The letters of Drs. Jukes and Still criticizing the focus on DDT in the November *CALIFORNIA MEDICINE* (devoted to Man, Medicine and Ecology) are interesting and provocative. Since my remarks about DDT in the *Overview* article were based to some degree on articles by Drs. Rudd and Audy in that same issue, I have asked them each to reply, and their comments follow.

I would like to add further comment of my own. The views of Drs. Jukes and Still reemphasize two points which I had hoped that the issue on Man, Medicine and Ecology had brought out and made clear: (1) homocentric thinking is often inconsistent with ecological fact; and (2) too often we look at only one side of the coin.

On the first point I would paraphrase John Donne's immortal line that "no man is an island" to read: "no species can live alone, technological man not excepted." Technological man is a clever fellow who likes to think he is in control, but he is subject to the same natural laws as all other species. Human beings need other "beings" . . . animal, plant, bacterial, etc.: our ultimate survival will depend upon a balanced life-support system on our planet and not simply upon the control of malaria or any other single human disease. This is not to argue against human disease control, but to urge enlightenment in the choice of agents and understanding of the various ecological implications. Thus while we practice insect control with persistent poisons for man's health and comfort we must be aware that we are destroying (or loading with poison) the food source of other species which may be very valuable to us.

Furthermore, to argue that DDT has no direct harmful effects upon man (a moot point, incidentally) is to beg the question: whether or not DDT has harmful effects upon earth's life-support system—which includes man's—is the issue.

On the second count (covered in part by Dr. Rudd below), I think that most people are well aware of the effectiveness of DDT in lowering human mortality and morbidity from malaria (and, as Dr. Still notes, promoting a population explosion in Malaysia). We also know about its various other "virtues" (*i.e.*, cheapness, ease of production, etc., etc.). If DDT were a specific for malarial control and if it were itself subject to



control, it might possibly be considered the panacea that both Jukes and Still appear to consider it. But DDT is neither a specific nor subject to control: it has a lot more to it. DDT is a broad spectrum, persistent, fat-soluble biocide which, once broadcast, enters the biosphere: it becomes incorporated into food chains, magnified with each trophic exchange and deposited in increasingly concentrated amounts into a number of forms of life. (To date, no one has found any way to remove it from any species, let alone any biotic or nonbiotic community.) DDT is furthermore extremely susceptible to meteorological and geological transport and is distributed widely by wind, rain, run-off via water courses, etc. It would be good if we could take "suitable precautions" in the use of DDT as Prof. Jukes proposes, but no one has defined scientifically what these "suitable precautions" should be.

Because of its cheapness and effectiveness in killing "pests," we have poured billions of pounds of DDT into the ecosphere (to use Lamont Cole's coined word) in an enormous uncontrolled global experiment. The long-range results of this experiment are still not understood. It is time we make a point of understanding them, for we are leaving a dubious legacy to our children who will have to live or die with these and the results of similar uncontrolled environmental experiments.

One further note: the Sarawak cat story to which Jukes refers was used for its particularly dramatic illustration of the inadvertent poisoning of the wrong species by a biocide. It is unfortunate that the story as related compounds an old mistake and implicates the wrong poison (see Audy below). But whether it was dieldrin or DDT (comparable poisons, incidentally) that killed the cats and whether by direct or indirect ingestion, the moral of the story remains true.

In conclusion, I wish that I could share Dr. Jukes' and Dr. Still's confidence in DDT. I wish I could reaffirm Browning's lines: "God's in his heaven—All's right with the world." But I can do neither; I continue to feel uneasy. The species which appear to be most endangered around us are most often top predators. Man is the topmost predator of all. As physicians, we have an enormous ecological job cut out for us if we are to keep him healthy and help him survive.

EDGAR WAYBURN, M.D.  
San Francisco

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*To the Editor:* My first response to Dr. Jukes' reasoned criticism of my repetition of the cats-killed-by-DDT story is to say *touché!* I wrote my article, "Man-made Maladies and Medicine," in too much of a hurry, while travelling abroad, and did not check that story. It seems that the biocide concerned was dieldrin. Dr. Jukes' calculations refer to a low toxic level of DDT to cats in acute studies and I will accept that cats would not be killed acutely by eating either wall-geckoes or cockroaches, nor, doubtless, are they easily killed chronically. But what are the prospects for chronic poisoning following "biological magnification"—a cat eats one rat that has already eaten a hundred cockroaches in its lifetime (and I am sure that it is the rats that eat most of the cockroaches and not the cats—but cats and rats do eat wall-geckoes). This one rat saves the cat two or three welcome minutes of cockroach chasing over the span of time it is getting its chronically lethal dose. Moreover, the rat may have absorbed DDT from another source and may have eaten a thousand cockroaches, ants, beetles, grubs, and other choice morsels fallen from the thatch. Also the healthy laboratory cats used in toxicity trials are very different from the scrawny half-starved almost feral cats that frequent *kampongs*.

Furthermore, what do we know about effect on feline reproduction (allowing that cats do not lay eggs with shells) and litter survival? What is the effect on a population over generations? I have been unable to get a satisfactory answer, but I do know that we *might* be surprised.

In Chiapas and Oaxaca, and I understand widely over the rest of Mexico, antimalarial biocide sprayers are jocularly known as *matagatos* or cat-killers by villagers. I am told that this is because their activities have been widely associated with noticeable die-off of cats. I was also told that the biocide concerned was DDT but my informants (who admitted that dieldrin was also used at times) may have been mistaken. I shall follow this up and perhaps Dr. Jukes or a reader can tell me more. The story behind this nickname helped me to accept the Borneo cat story uncritically.

Dr. Jukes is however absolutely right in drawing attention (a) to the great boon that DDT

has been to us—most troubles have really been due to excessive use, for wise use demands great care and we might have been better off if DDT cost ten times more than it does; and (b) to the facility with which people may both repeat and embellish information uncritically. I am reminded of the British World War I story about the weaknesses of the field telephone. An urgent message, "Send reinforcements. We are going to advance," finished up as "Send three and fourpence. We are going to dance." That is just how information often gets transformed nowadays.

J. RALPH AUDY, M.D., PH.D.  
*Director, G. W. Hooper Foundation  
 San Francisco*

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*To the Editor:* Professor Thomas Jukes has been a perennial letter-writer in defense of DDT. I've never fully understood why. His facts are accurate as far as they go, but his premises and judgments can easily be debated.

The most revealing thing about Professor Jukes' letter is that he apparently does not grasp the full meaning of CALIFORNIA MEDICINE's Ecology issue. For one thing, I agree with him on the question of residue levels in human milk. I see no evidence of harm. What he overlooks however is that no one wants these residues, particularly without either control or knowledge of their intake. That is the issue. Applied toxicology is not simply an LD<sub>50</sub> extrapolated. Nor does simple arithmetic extrapolation remove the food-chain effects as in the "Sarawak" example he in effect ridicules. We do actually have DDT and a number of other residues existing in the general environment in both physical and biological components. The documentation is impressive. So also are the biotic complications, being all too slowly revealed. The suggestion is now very strong that the "threshold concept" characterizing much toxicological study and monitoring activity is an improper basis for social judgment. For too long toxicologists and biochemists have defined their studies narrowly. They should as well consider the "Uncertainty Principle" and when recommending chemical prescriptions, for whatever good purpose, incorporate the total potential of the recommendations. DDT is an excellent example of a chemical in use defined and recommended on fractional grounds.

The number of governments, national and provincial, which have banned or restricted DDT usage is increasing. No one doubts the fractional value of DDT; many doubt its value when the totality is considered.

Debate can be continued almost indefinitely. I suggest however that Professor Jukes read carefully the entire issue of CALIFORNIA MEDICINE's November issue and react as well to other "signs of the times." The current humanistic up-welling exemplified in ecological awareness is by no means casual and shallow.

ROBERT L. RUDD, PH.D.  
*Professor of Zoology  
 University of California, Davis*

## Ecological Health

*To the Editor:* You will recall that I had implied in my earlier correspondence with you about your September editorial that the application of your "new ethic" as a solution to the alleged overpopulation problem was anti-democratic and anti-humanitarian. And that you had implied, in your personal letter to me (10/20/70), that I had somehow misunderstood your "intent" in that editorial. But as if to verify the accuracy of my initial assessment of the ultimate implications of your ideology, and as if to answer my initial criticisms negativistically; you have subsequently pursued this same subject of "wherein lies the physician's responsibility" in the far-reaching implications of coercive population control, in your November editorial, in which you reiterate, even more strongly, the totalitarian thesis presented in your September editorial:—that the "ecological realities" will impose "further restrictions on personal freedom" (e.g., the freedom "to procreate"); that "universal compliance with certain decisions" will be necessary; that "traditional value systems" (ethics?) may need to be replaced; that some people will predictably resist these restrictions in favor of "their own ideas of freedom"; that such "emotion must be harnessed"; and finally, that physicians must prepare to "advise" patients and "even world governments" along these lines.



And as if to further verify the totalitarian slant of your ideology; in this same November editorial, you have extolled, without any apparent qualifications, as being "fascinating and authoritative," all of the articles which make up what you call "an excellent and unusual symposium," in this same issue of CALIFORNIA MEDICINE. Among those authors for whom you have such high praise are these:

Garrett Hardin, Ph.D.:—who suggests that we physicians should feel ashamed of the "misery" we have caused in "saving lives" over the years; but that we might be forgiven for such well-intended mischief, presumably only because we acted out of "ignorance" of the harm we were doing. He hints that we physicians might redeem ourselves if we will only help "to create a new climate of opinion" for the public support of *measures stronger* than "*voluntarism and persuasion*" in the "community control of breeding." He believes we should at present push only for voluntary abortion and sterilization until the time is ripe for "positive community control of the number of children produced." And until we arrive at this final dictatorial stage, he believes that we might control a person's right to have children by issuing a limited number of "green stamps . . . which could be bought and sold in the market, like stock options." Furthermore, he believes we should replace ". . . every man's death diminishes me. . . ." with a saying, which he asserts is "nearer the truth": i.e., "Every babe's birth diminishes me."

Kingsley Davis, Ph.D.:—who calls this the "century of the population (people?) plague"; who puts "solicitude for collective welfare" ahead of individual rights; who deprecates reduced mortality due to the progress of modern medicine because it has made "biological adaptation unnecessary" by reducing the "selective pressure" (or the survival of the fittest mechanism?) of "genetic evolution"; who *strongly disapproves* the U.N. General Assembly policy that the family should be encouraged as the basic unit of society and that parents should have the exclusive right to determine freely and responsibly the number of children they wish to bear and support; and he obviously *approves* "the painful social reforms," that would be necessary to reduce people's desire for children.

J. Ralph Audy, M.D., Ph.D.:—who disparages the "ingrained" attitude of the medical profession

that "the mission of medicine is to combat disease and stave off death"; who feels that we spend too much time with "unhealthy people who are repeatedly getting sick" and that we are too pre-occupied with sick individuals "instead of the public at large." In fact, he believes that "we would all gain greatly . . . if we were to take the . . . in fact almost revolutionary view that the positive physical, mental, and social health of the *public* (rather than patients individually?) comes before anything else. . ."

Now, Dr. Watts, I would like to put to you this question:—Having reviewed the foregoing excerpts of opinions (which you may have previously missed, inadvertently) from the articles which you published with such fanfare in the November issue; and having noted how they conflict with the spirit, ethic and attitude of almost all physicians; would you at this time like to add some sort of qualification to the enthusiastic endorsement you initially lavished on these articles, as to their authoritativeness, etc.?

JAMES H. FORD, M.D.  
Lynwood

## Methadone and the Heroin Addict

*To the Editor:* The article entitled "Methadone Maintenance for Opiate Dependence" by John C. Kramer, M.D., which appeared in the December, 1970, edition of CALIFORNIA MEDICINE, serves a useful purpose in familiarizing its readers with the concept of methadone maintenance.

For those readers interested in a statistical report of one of the oldest of such programs, I refer them to an article in the April, 1970, issue of the AMERICAN JOURNAL OF PSYCHIATRY by Perkins and Bloch. However, it is almost impossible to draw meaningful conclusions from any statistics on this subject, because the rationale for methadone maintenance is that it will reduce the amount of crime committed by addicts. But there is no way of knowing what crimes *do not get committed* by individuals receiving methadone which *would have been committed* by these addicts had they not been treated with methadone.

One would like to see the incidence of burglaries and robberies decrease in a city with a methadone maintenance program, but everywhere the crime rate is increasing, and there are so many other variables which affect the crime rate that it would be impossible to separate out the effect of a methadone maintenance program from such other factors as the employment rate, the increased number of policemen, the job training and antipoverty programs, the speed with which criminal cases are processed through the courts, the sentences meted out by the courts, and the efforts made by citizens to protect themselves from crime.

But the most important question I wish to raise is the last one discussed by Doctor Kramer, namely, what will be the effect of methadone maintenance on the long-term problem of heroin addiction?

It seems logical to assume that if opiates are made available for the maintenance of addiction, then the number of individuals who will avail themselves of these opiates will increase. If methadone maintenance is available, then there will be little inducement, for those so inclined, to restrain themselves from using, and becoming addicted to, heroin. Many who now hesitate to use heroin would be less hesitant to do so if they knew that addiction to heroin would eventually result in maintenance on methadone, rather than its resulting in a ruined life.

The experience in Great Britain is that since 1956 the number of heroin addicts has increased several fold, and this increase may well be due, in large part, to the fact that in Britain heroin maintenance has been available.

YEHUDA SHERMAN, M.D.  
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## A Student's Comments

*To the Editor:* A year ago I received a gift subscription to CALIFORNIA MEDICINE. I wish to express my thanks to you and the Women's Auxiliary for that subscription.

During the year I have read CALIFORNIA MEDICINE for the political, academic, and current issues it has covered. By political issues I mean the insight given into the workings and make-up of the CMA, or at least of those members of the CMA whose opinions have been expressed through CALIFORNIA MEDICINE.

As I entered medical school, my opinion of the CMA was shaped by what I saw around me, i.e. the poor state of medical care delivery and the restrictive nature of medical education in California. In my eyes, and I think in the eyes of a great number of my colleagues, the troubles in California were due in no small part to myopic, self-serving doctors and their organized voice, the CMA. And although I am still not convinced that such is not the case, I was surprised to learn that a substantial number of California doctors are now actively and vociferously working for constructive changes in California medicine.

Academically, CALIFORNIA MEDICINE provided numerous articles throughout the year that were both interesting and enlightening to me as a medical student. I was not surprised when, in a microbiology class, we received a reprint from a recent article in CALIFORNIA MEDICINE.

Finally, the numerous "current issue" articles were especially interesting. Discussions such as "Relevance in Medical Education," October's special article on medicine in the black community and November's ecologically-oriented issue are three examples of current topics which are of great interest to medical students and certainly deserving of space in CALIFORNIA MEDICINE.

I hope you will continue to offer this complimentary means of communication and education to other medical students because it is sorely needed and it is effective.

As an example, I was surprised to find myself defending CALIFORNIA MEDICINE and the CMA when a colleague said to me, "You mean you actually read that conservative bunk?"

Have I been won over? Am I converted? Hardly, because I can still see numerous flaws in the CMA, its journal and its physicians. But the fact remains that something of a bridge-foot-bridge though it may be—has been established between the old world and the new world physician in California.

XAVIER J. CARO  
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School of Medicine  
Class of 1973*



# Considerations in Devising an Overall Health Plan

RUSSELL B. ROTH, M.D., Erie, Pa.

*Speaker, American Medical Association House of Delegates*

EDITOR'S NOTE: This report was prepared by Dr. Roth and submitted to the Department of Health, Education, and Welfare. It was transmitted to the House of Delegates in November 1970 for their information. It is presented here in the belief that it will be of great interest to the readers of CALIFORNIA MEDICINE.

## Thesis:

The principal resource for meeting the medical service needs of the Nation is the existing supply of practicing physicians.

1st priority is for using effectively those practicing physicians we now have.

2nd priority is to do those things which may be done to increase the productivity of physicians.

3rd priority is to augment the number of physicians.

4th priority is to use the physician effectively in his role as a conservator of expenditures by and in behalf of his patients.

Considerations in respect to the 1st priority (effective use):

There has been a substantial "flight from practice," and especially from general practice, which has intensified our problems in the delivery of medical service. The factors which have caused this exodus from direct patient care should be recognized and, to the extent possible, eliminated. There has also been the disturbing fact that although new physicians are being trained at a rate well exceeding the rate of general population growth, these young doctors are not being motivated to enter into direct patient care in the areas

of greatest need. If we wish to hold on to our current supplies of active practitioners and to increase them in a rational fashion there are certain things that we should do, and a number of things which we assuredly should not do.

1—In the existing climate of the United States, efforts to regiment, conscript, or apply economic sanctions to the medical profession are destined to make matters worse rather than better. They have the effect of driving even more physicians from active practice into research, teaching, administrative medicine, more narrow specialization or premature retirement.

2—Promises on the part of government that practicing physicians will deliver even more health service to beneficiaries than they are now able to produce under stress conditions force still more physicians to seek refuge from the pressures.

3—The practicing physician is confronted with increasing costs of living and of doing business. In a generally uncontrolled economy, measures which would freeze the income levels of physicians, eliminating their ability to adjust to the economic environment are discriminatory and lead to still further departures from active practice.

4—The individual physician has limited opportunity or capacity to respond to over-all societal demands. These responses are best made by physicians collectively, acting in concert through their professional associations. It is in the best interests of the Nation that professional organizations be aided and abetted in their co-

operative efforts. To denigrate them and to give them adverse tax treatment reduces their capacities and their resources for constructive input.

5—It has been proposed in several legislative bills that bonus dollars will motivate physicians to establish practices in rural and urban shortage areas. The fact is that large numbers of physicians who have been providing service in those areas leave lucrative practices for less rewarding circumstances in which the offsets are such things as personal and family security, improved educational facilities, or a lessened pressure of patient demand.

6—Prepaid comprehensive group practice has been “discovered” as a potential answer to most of the delivery problems. Rechristened “Health Maintenance Organizations,” these arrangements for practice are offered as a panacea without recognition of the fact that such groups have been encountering serious problems of their own, that many patients do not wish to enroll in such plans, and that many physicians have no interest in practicing in them. The many variations of this approach deserve support as competitive mechanisms with a chance to prove such superiorities as they may develop in respect to quality, efficiency and economy; but to attempt to force all physicians into a rigid pattern of salaried group practice could be the most destructive move made by government.

7—Plans which would base the entire delivery system of medical service upon “primary physicians” with responsibility for channelling patients and regulating payments to consultants, specialists and the like betray a lack of understanding as to how medicine is practiced.

8—The willingness of physicians to participate in and to be subject to peer review in respect to the quality and quantity of their services and the charges made therefor are encouraging. This should be supported, not discounted. The prospect of evaluation by non-medical reviewers, or medical reviewers hired by non-medical agencies is a strong deterrent to cooperation.

In summary, to keep physicians in active practice, rather than to disperse them, government should abandon emphasis on prepaid comprehensive group practice although it may still support it. It should uphold the principle that a physician should be expected to charge his usual fees to all patients and should depend on a strengthened system of peer review to guarantee that such

usual fees will conform with customary fees and be kept within the ranges of what can be defined as “reasonable.” Mathematical formulae for freezes and arbitrary percentiles should be abandoned. It should probably be accepted that highly trained physicians cannot be attracted into practice in rural areas or in many slum areas, and alternative mechanisms for the provision of adequate medical service should be developed.

Considerations in respect to the 2nd priority (increased productivity):

1—There is, in general, little opportunity to increase the productivity of the average practicing physician by simple extensions of his working hours. Actually current enthusiasm for group practice formulae seem to be retrogressive inasmuch as it is represented to the physician who is currently working 60-70 hours per week that under group practice arrangements he may reduce this to 50 or less hours per week. Scattered figures may be cited to support the idea that 100 physicians in solo practice actually provide service to more patients per week than do 100 physicians in group practice of any type.

2—The multiple experimental programs of Medex, Duke University, the American Urological Association, and scores of others to develop support to the practicing physician deserve subsidy and assistance. At the same time serious attention must be paid to the medical practice acts of the several states, to factors of professional liability, insurance coverage, and the like.

3—Restrictive provisions in such programs as Medicare and Medicaid which make it economically unfeasible for physicians to delegate to others—especially to interns, residents and office assistants—the provision of appropriate services should be eliminated or readjusted.

4—Government has taken an unproductive and adverse position in respect to those physicians who have appeared to earn “too much” money from Federal and State programs. Instead of the antagonistic approach of questioning the financial “take” by such persons focus should be on requesting “peer review” of the quality of care offered by these mass producers. It may be good.

5—Many physicians are dissuaded from, or become disenchanted with, efforts to provide medical service for Federal and State program beneficiaries because of relatively low compensation, excessive paper work, and an exposure to adverse publicity because of payments



received. This should be corrected. Physicians willing to devote themselves to this type of work in volume should be praised rather than denigrated for their efforts.

Consideration in respect to the 3rd priority (augmentation of physician numbers):

1—Support to the educational roles of medical schools should be clearly separated from support to medical research so that the latter is not used as a subterfuge for the building of a medical school faculty, or the underwriting of medical school operations.

2—As much attention should be devoted to keeping in clinical practice the physicians we have, as [is devoted] to the training of more physicians.

3—A positive program of public relations dedicated to making the clinical practice of medicine attractive to oncoming generations of young Americans would be more productive than a campaign to picture physicians as entrepreneurs requiring regimentation and control.

4—Serious attention should be given to the problem of professional liability insurance and the jeopardy in which the practicing physician finds himself today. It is no small matter that the new physician finds that he must pay from two to ten thousand dollars per year in malpractice insurance premiums before he feels safe to treat his first patient. It is equally important to recognize that many active practi-

tioners are being forced from practice by the inability to purchase at any reasonable figure adequate liability insurance. The answer does not lie in finding new "carriers" for the insurance. It lies in legal reforms governing liability.

Considerations in respect to the 4th priority (conservator of public expenditures):

1—"Peer Review" is the governing concept which requires support. To dilute it with lip service to consumer representation is not helpful. The medical profession needs to be supported in the outstanding progress which it has made in the past decade in the perfection of peer review techniques.

2—Indoctrination in peer review should be looked upon as a proper role of National, State and County Medical Societies for incorporation into medical school curricula and hospital intern and residency training programs.

3—Techniques of education for the practicing physician in the relationship between hospitalization, physician orders and prescribing practices and the expenditures mandated for patients or those who pay their bills should be advanced.

4—Considerable attention should be given to the thought that when a physician is salaried, or otherwise divorced from the fee-for-service method of compensation, he is insulated from a specific interest in how his services or his authorizations for service have impact upon the economics of medical care.

### TESTING FOR SENSORY PARESIS WITH VOCAL CORD PARALYSIS

"For a long time I never tested for sensory paresis or paralysis when I saw a patient with a paralyzed vocal cord. But a simple test is to dress a curved laryngeal applicator with cotton and test the sensation of the epiglottis, the aryepiglottic folds, and the false and true cords. . . . Care must be taken not to touch the base of the tongue during this procedure since we want to test primarily the tenth nerve and not the ninth. We test first one side and then the other; and we will find not only unilateral but sometimes bilateral lesions."

—DAVID W. BREWER, M.D., Syracuse

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# The Medi-Cal Program — 1966 - 1971

A Socio-Economic Report of the Bureau of Research and  
Planning, California Medical Association

**NOTE:** *Estimates and projections contained in this Report are based on information made available in mid-1970. More current data suggest that they very probably have been understated. Hence, the reader should exercise caution in using such figures.*

CALIFORNIA'S MEDICAID PROGRAM (health care services to recipients of public assistance and to the medically needy) was implemented as Title XIX of the Social Security Act on March 1, 1966, having superseded the earlier Public Assistance Medical Care and Medical Assistance for the Aged Programs. Although the proportion varies among the various states which participate in the program, in California's case funding provided by the federal government is equal to approximately 50 percent of the total cost of care. State and county governments share the remainder in amounts which are computed under various provisions of the Welfare and Institutions Code. The declared goal of the program, known in the State as Medi-Cal, is to provide by 1977 all necessary health care services to persons classified as medically indigent.

## Five-Year Expenditure Patterns

By the end of the current fiscal year (July 1970-June 1971), for which figures have already been projected, total cost of care will have increased by more than 532 million dollars, or 104.9 percent, during its five years of existence. During the same period, the total number of persons eligible will have increased 76.7 percent.

Table 1 shows the annual cost of care, by type of item or service, for each of five years since the program went into effect, as well as the percent

increase in cost between 1966-67 and projected 1970-71 for each. It is noteworthy that expenditures for drugs, for hospitals and for nursing home care have each more than doubled in the five-year period. Costs for hospitalization have consistently accounted for more than one third of the total budget for cost of care. New regulations restricting hospital and nursing home utilization became effective on July 1, 1970, in an effort to keep the costs of these two services within the budgeted figures. The component listed as "other," which includes optometrists, opticians, podiatrists, payments to State Hospitals, home health agencies, laboratories, medical transportation, therapists and other providers and services, shows an increase of some 105 percent for the five-year period. Three of these four components show greater percentage increase during the five fiscal years ending June 30, 1971, than does the total for all services combined. The fourth component, Drugs, shows a percentage increase only slightly below that for all services.

Payments for dental services and for physician services rose least rapidly during these five years. Although consistently accounting for approximately one-fifth of the total cost of care, payments to physicians have shown a slight relative decline during the period. Projected dollar increases are based on anticipated total patient caseload and do not allow for increased costs of care for each patient.

Title XVIII (B) Buy-In costs, which have more than doubled in the four years for which figures are available (1967-68-1970-71), are shown separately and not included in the over-all total. Expenditures for this item are controlled by the number of persons covered by Medicare who are

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco, Ca. 94102.



**TABLE 1.—Medi-Cal Program: Annual Expenditures by Service Component in Five Fiscal Years through June 1971 (in millions of dollars)**

Service component	1966-67		1967-68		Fiscal year 1968-69		1969-70 <sup>1</sup>		1970-71 <sup>2</sup>		Percent increase 1966-67 to 1970-71
	Dollars	Percent	Dollars	Percent	Dollars	Percent	Dollars	Percent	Dollars	Percent	
Physicians .....	\$110.2	21.7	\$122.5	21.7	\$147.8	19.6	\$165.9	19.1	\$206.5	19.9	87.4
Drugs .....	37.8	7.5	43.7	7.7	56.8	7.5	58.6	6.7	76.3	7.3	101.9
Dentists .....	33.1	6.5	22.9	4.1	38.2	5.1	46.1	5.3	58.2	5.6	75.9
Hospitals .....	174.2	34.3	204.4	36.3	277.5	36.7	306.8	35.3	377.0	36.3	116.4
Nursing homes .....	105.6	20.8	128.6	22.9	161.6	21.4	203.2	23.4	225.9	21.7	114.0
Other <sup>3</sup> .....	46.6	9.2	41.3	7.3	72.9	9.7	88.7	10.2	95.9	9.2	105.8
Total .....	507.5	100.0	563.4	100.0	754.8	100.0	869.3	100.0	1039.9	100.0	104.9
Title XVIII (B) Buy-In ..	<sup>4</sup>		\$12.8		\$14.8		\$17.9		\$26.2		104.1 <sup>5</sup>

<sup>1</sup>Estimated

<sup>2</sup>Proposed

<sup>3</sup>See text for items and services included

<sup>4</sup>Figures not available

<sup>5</sup>Increase from 1967-68

**TABLE 2.—Numbers and Percents of California Population Eligible for Medi-Cal Coverage and Annual Expenditures for All Services and for Physicians' Services Per Capita and Per Eligible, Five Fiscal Years through June 1971**

Fiscal year	Population (in thousands)			Average annual expenditures			
	Eligible for Medi-Cal			Per capita		Per eligible	
	Total	Number	Percent	Total	Physicians' services	Total	Physicians' services
1966-67 .....	19,070.7	1298.2	6.8	\$26.61	\$ 5.77	\$390.93	\$84.83
1967-68 .....	19,408.0	1475.7	7.6	29.03	6.30	381.71	82.83
1968-69 .....	19,705.0	1643.6	8.3	38.30	7.51	459.24	90.01
1969-70 .....	20,008.0	1856.9	9.3	43.45	8.30	468.15	89.42
1970-71 .....	20,329.0	2294.5	11.3	51.15	10.16	453.22	90.01
Percent change 1966-67 to 1970-71 .....	6.6%	76.7%	—	92.2%	76.1%	15.9%	6.1%

also eligible for Medi-Cal assistance and the Buy-In costs as established by the Social Security Administration.

### Increase in Number of Medi-Cal Eligibles

As can be seen in Table 2, an increase of about one million persons (76.7 percent) in the average monthly count of beneficiaries—from 1.3 million during 1966-67 to an estimated 2.3 million for the 1970-71 year—is anticipated. During the same five years California's population will increase by about 1.3 million persons (6.6 percent) according to estimates of the California Department of Finance.

Despite this relatively rapid increase in population—an average of 1.6 percent each year—the increase in the number of beneficiaries under Medi-Cal will far exceed that of the total popu-

lation. During the 1966-67 fiscal year, one person in fifteen in California received Medi-Cal benefits; during 1970-71 it is projected that this proportion will be one person in eight.

Total dollar payments for cost of care per capita and per Medi-Cal eligible are also shown for each year, together with dollar payments for physicians' services. Table 2 shows a percentage increase in total payments per eligible of approximately 16 percent, while payments for physicians' services per eligible are expected to increase just over 6 percent during the five-year period.

It is interesting to note that the average cost of the program, when shown on a per capita basis for all Californians, is expected to increase from an annual cost of \$26.61 to \$51.15, or 92.2 percent. As already indicated, this increase is primarily attributable to an expanding caseload, rather than

TABLE 3.—Total Medi-Cal Costs and Administrative Costs for Three Types of Agencies, Five Fiscal Years through June 1971 (in millions of dollars)

Fiscal year	Total Program Costs <sup>1</sup>	Total	Administrative Costs			Percent Administrative Costs
			State Government	Agency Fiscal Intermediaries	County Government	
1966-67 .....	\$ 507.5	\$21.0	N/A	N/A	N/A	4.1
1967-68 .....	563.4	28.1	N/A	N/A	N/A	5.0
1968-69 .....	754.8	36.6	\$ 8.0	\$14.6	\$14.0	4.8
1969-70 .....	869.3	42.0	8.7	20.3	13.0	4.8
1970-71 .....	1039.9	53.6	15.1	21.8	16.7	5.2

N/A: Not available

<sup>1</sup>Excludes costs for Title XVIII (B) buy-in

to increased expenditures per eligible. The per capita amount allocated to physicians' services is expected to increase at a lower rate of 76.1 percent, from \$5.77 to \$10.16.

### Administrative Costs Shown for Three Types of Agencies

Table 3 shows administrative costs of the Medi-Cal program for the years July 1966 through July 1971 in dollar amounts and as a percentage of total program costs. The years 1968-69, 1969-70 and 1970-71 are further delineated to show administrative costs by the State, the counties and the fiscal intermediaries. The total cost of administration has generally remained in the area of five percent. This proportion is expected to increase to 5.2 percent in 1970-71 for reasons which will be explained later.

County operations are concerned with the determination of eligibility by the various county welfare departments under the direction of the State Department of Social Welfare. These welfare agencies certify the eligibility of persons for medical assistance benefits.

Fiscal intermediaries include California Blue Shield, Hospital Service of California and Hospital Service of Southern California. It is estimated that these three intermediaries will pay 30.2 million claims during 1969-70 at an average administrative cost of \$1.34 per payment. The projected number of claims for 1970-71 is 35.4 million with an estimated average administrative cost of \$1.20 per payment.

The State administration of the Medi-Cal program involves the State Department of Health Care Services, which both administers the program and coordinates the activities of the State Departments of Mental Hygiene, Public Health

and Social Welfare in their involvement with the Medi-Cal program. The sharp increase in this portion of administrative costs anticipated for the 1970-71 fiscal year is due to an increased fund request by the Department of Health Care Services (DHCS). The DHCS administrative budget has been increased from 5.7 million dollars for 1969-70 to 11 million dollars for 1970-71—a jump of 92 percent—in anticipation of realizing longer term program savings. The largest single item in this proposed increase is 4.5 million dollars for the 1970-71 support of a pilot project of a management system which would program, test, develop and implement innovative concepts in the program on a prototype basis in two counties. The project will be implemented in three phases:

	Maximum cost
1. Design Stage—7 months	\$1,240,000
2. Development—11 months	2,870,000
3. Implementation—6 months	1,660,000
Total	\$5,770,000

### DHCS Adjusts in Five Fields to Save Money

The Department of Health Care Services indicates that its proposed budget for 1970-71 provides savings of some 49 million dollars in the cost of care by adjustments in five general classifications,\* as follows:

1. *Intensify control of hospital utilization* by requiring submission of the hospitalization request ten days in advance of admission with an estimate of the length of stay for all non-emergency admissions. Notification of emergencies would be required within 24 hours of admittance. At present non-emergency hos-

\*These five fields represent the program outline at the time this report was prepared. Should changes have been made subsequently, the expected effects would be changed accordingly.



pitalizations represent 20 percent of all hospitalizations. The Department estimates it can control ten percent of the non-emergency hospitalizations and thus effectuate savings of 17 million dollars.

2. *Tighten eligibility requirements for medically needy persons* by establishing a system of State certification (currently counties handle such certification), and by reducing personal property exemptions from the present \$1,500 to \$600 for a single person and from \$3,000 to \$1,200 for a family. The savings resulting from this proposal are estimated to be \$13 million.

3. *Establish a schedule of maximum allowance for outpatient services.* The Department proposes to establish a Schedule of Maximum Allowances for outpatient services provided through hospitals, clinics, neighborhood health centers and other institutions. The program savings resulting from this proposal are estimated to be 5 million dollars.

4. *Establish 14 medical-social review teams* to evaluate the needs of each person in a nursing home or mental institution to determine whether or not the patient needs that level of care or could be moved to a lower cost inter-

mediate care or residential facility.\*\* The establishment of these medical-social review teams will serve to comply with the Social Security Act Amendments of 1967 requiring periodic inspections to be made in all skilled nursing homes and mental institutions within the State by one or more medical review teams composed of physicians and other appropriate health and social service personnel. Savings of 12.4 million dollars are expected to accrue from the operation of these review teams.

5. *Restricted utilization of psychologists and special duty nurses will be instituted.* Rather than including psychologists as individual providers, the program is recommending that these services be provided as part of a team, as found in an institutional setting. The need for special duty nursing is greatly diminished with the advent of intensive care units in hospitals; where it continues to be essential, it can be provided in a controlled hospital environment. Savings of 2 million dollars are anticipated.

\*\*\*Intermediate care facilities,\*\* as such, do not yet exist in California. However, applicable licensing regulations have been adopted and the State Health Planning Council has developed guidelines for pre-licensing approval of such facilities. The state hopes that skilled nursing homes will convert some of their beds to intermediate care within the next year.

## CATHETER SITES FOR MONITORING SHOCK

By what route do you insert the catheter if you want to monitor central venous pressure in a patient in shock?

"For the physician or surgeon who is very much at home in the critical care environment, the subclavian route, I think, is a good route. You can get into it rapidly with some skill. You can maintain the catheter away from sites of interference. But, on the other hand, for the occasional operator, that area is fraught with some dangers — namely, pneumothorax, possibility of penetrating the aorta, and so on. So that for the occasional operator, I would prefer seeing the catheter placed by way of the brachial vein."

—MAX HARRY WEIL, M.D., Los Angeles

Extracted from *Audio-Digest Surgery*, Vol. 16, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# General Highlights of Cardiac Auscultation

JOSEPH K. PERLOFF, M.D.

*Material Supplied by the  
American Heart Association*

THE PRACTICAL USE of cardiac auscultation requires an understanding of certain elementary principles. First, auscultatory events must be heard before they can be interpreted; accordingly, the technicalities and techniques of auscultation are paramount. Second, recognition of the various heart sounds, especially the first and second sounds, defines systole and diastole and establishes the timing of the different phases of the cardiac cycle. Third, the timing of murmurs can readily be accomplished once the phases of the cardiac cycle are defined. The following remarks will touch on each of these three principles.

*Technicalities and Techniques.* The chain of success consists of a number of links. The instrument of auscultation is the stethoscope that was introduced by Laennec in 1819. The ideal stethoscope is yet to be devised but good instruments are available and certain guidelines are useful in their selection. Both a bell and a diaphragm are necessary, the former for the low frequency ranges and the latter for the high. Connecting tubing should be relatively firm and single; double tubes are acoustically less efficient and cause extraneous noise when they touch or rub together. The overall length of the entire stethoscope should be about 22 inches. The binaural ear pieces should be relatively large so that they occlude the external auditory canals and do not uncomfortably enter them. Finally, all connections must be airtight in order to avoid loss of sound by leakage.

Dr. Perloff is from the Department of Medicine, Georgetown University School of Medicine, and the Division of Cardiology, Georgetown University Hospital, Washington, D.C.

The next link in the chain is the sensing device, that is, the human ear which can be trained to sense the broad range of frequencies emanating from the heart and blood vessels. It is encouraging to know that the ear is more efficient than the phonocardiogram in recognizing high frequencies such as the soft murmur of aortic incompetence. The ears are all-important since even the best stethoscopes do not amplify sound but merely transmit it to the ears with relatively little loss. Perhaps the most important link in the chain is the interval between the stethoscopic ear pieces, namely, the human brain. The brain interprets what is heard, and in order to do so effectively it must be programmed by years of experience. Once these technical links—the instrument, the sensing device, the interpreter and the programming—are forged, we can turn attention to the auscultatory technique itself.

Auscultation should be conducted in a quiet examining room that is free of ambient noise and that has a temperature high enough so that the patient does not shiver. The patient must be relaxed and comfortable and the examiner unhurried. Examination should be done with the patient in various postures, such as supine, prone, left lateral decubitus, sitting, leaning forward, standing, or squatting. Respiratory patterns should also be appropriately selected including quiet or arrested breathing for routine auscultation, full held expiration for the soft murmur of aortic incompetence, or normal or exaggerated respiratory excursions for the behavior of the second heart sound or for certain right-sided events. Physical and pharmacologic interventions are useful and include coughing, effort, squatting, isometric tension (squeezing the clenched fists), and certain vasoactive drugs especially amyl nitrite and pressor agents. When the bell of the stethoscope is applied with varying degrees of pressure, a relatively broad range of frequencies can be elicited. When the bell is touched lightly to the skin, low frequencies are heard (soft third heart sound); when high frequencies are paramount, firm pressure with the diaphragm is required. Palpation should precede auscultation so that the stethoscope can be placed precisely at the most appropriate precordial sites. Finally, auscultation should not be confined to the precordium but should include the right chest, axillae, back, neck, flanks, abdomen, groins, and at times the eyeballs and skull.



*The Heart Sounds.* The normal heart sounds define the phases of the cardiac cycle and serve as standards by which abnormal heart sounds can be judged. The first heart sound is best assessed at the apex or lower left sternal edge and is either single or closely split. Splitting is usually confined to the lower sternal edge and is normally not heard at the base. Although analysis of the first heart sound provides helpful information, analysis of the second heart sound is far more useful and has been called the key to auscultation of the heart. Proper interpretation of the second sound assumes an awareness of its location, splitting and intensity. In the second left intercostal space there are two components, aortic and pulmonic, which are synchronous (or nearly so) during expiration and split during inspiration. A judgment regarding the intensity of pulmonary valve closure requires comparison with aortic closure when both sounds are heard simultaneously during inspiration. The comparative softness of the pulmonary closure sound is held responsible for its localization in the vicinity of the second left intercostal space, and the relative loudness of aortic closure accounts for its audibility at all areas. It should clearly be stated that  $A_2$  refers to aortic valve closure and  $P_2$  to pulmonary valve closure.  $A_2$  and  $P_2$  do *not* refer to the second heart sound in the "aortic" versus the "pulmonary" area; such use implies a complete misunderstanding of the origin of the two components of the second sound. Similarly,  $P_2$  by definition is a single sound caused by pulmonary valve closure, so the expression "split  $P_2$ " is a misnomer that should be abandoned.

The third and fourth heart sounds are best understood in relation to the two diastolic phases of ventricular filling. These sounds originate within the recipient ventricle, the third sound during the middiastolic filling phase and the fourth sound during the presystolic filling phase. Accordingly, a fourth heart sound implies sinus rhythm. Both sounds are low frequency events that are most readily heard with light touch of the stethoscopic bell.

The foregoing heart sounds — first, second, third and fourth—can either be normal or abnormal. The following sounds are, for all practical purposes, abnormal events.

Opening snaps characteristically originate in the mitral valve usually because of stenosis. The

snap is relatively high frequency, is heard not only at the apex but also at the sternal edge and base, and is best elicited with the stethoscopic diaphragm or firm pressure with the bell. Since the mitral valve must open before the ventricle can fill, the timing of the opening snap necessarily precedes the timing of the third heart sound.

Ejection sounds are high pitched, clicking early systolic events that originate in either the left heart (aortic valve or dilated ascending aorta) or right heart (pulmonic valve or dilated pulmonary trunk). These sounds tend to be heard at the base of the heart and should not be mistaken for split first heart sounds. The aortic ejection sound is well-heard at both the base and apex and with rare exception does not vary with respiration; the pulmonic ejection sound is well-heard in the second left intercostal space and often varies characteristically with respiration, getting selectively softer with inspiration and louder with expiration.

Systolic clicks must be distinguished from ejection sounds. The clicks are similar to ejection sounds in frequency but not in timing or chest wall location. Clicks generally originate in redundant mitral chordae tendineae; they are single or multiple, maximal at the apex, and begin in mid to late systole.

*Cardiac Murmurs.* A cardiovascular murmur is a relatively prolonged series of auditory vibrations characterized according to intensity (loudness), frequency (pitch), configuration (shape), quality, duration, direction of radiation and timing in the cardiac cycle. The timing of murmurs is particularly important since it serves as a basis for classification. Systolic murmurs are classified according to their time of onset and termination as midsystolic, holosystolic, early systolic, or late systolic. A midsystolic murmur begins after the first heart sound and ends before the second sound (aortic stenosis). A holosystolic murmur begins with the first heart sound, occupies all of systole, and ends with the second heart sound (classic mitral incompetence). Early systolic murmurs begin with the first heart sound, diminish in a decrescendo fashion, and end at or before midsystole (very small ventricular septal defect with early systolic shunt). Late systolic murmurs begin in mid to late systole and end with the second heart sound (mitral incompetence with late systolic regurgitation). Finally,

extracardiac systolic arterial murmurs originate in either systemic or pulmonary arteries. The existence of such murmurs emphasizes the importance of careful auscultation at nonprecordial sites.

Diastolic murmurs are classified according to their time of onset as early diastolic, middiastolic or late diastolic (presystolic). An early diastolic murmur begins with the second heart sound (aortic incompetence). A middiastolic murmur begins at a clear interval after the second heart sound (mitral stenosis with atrial fibrillation). A late diastolic murmur or presystolic murmur begins in the period immediately before the first heart sound (mitral stenosis with sinus rhythm).

The term *continuous* is best applied to murmurs that begin in systole and continue without interruption through the time of the second heart sound into all or part of diastole. Persistence of murmurs throughout the cardiac cycle is therefore not a requirement. Accordingly, a murmur that proceeds into diastole without stopping at the second heart sound is considered continuous whether or not it finishes before the next first heart sound. Continuous murmurs can be due to aortopulmonary communications (patent ductus), arteriovenous connections (systemic arteriovenous fistulas), or can be purely arterial (arterial constriction), or purely venous (venous hum).

#### ANTACIDS IN ULCER THERAPY

"There is so little difference between the various antacids. What's much more important is when they're given. Far too many people give antacids after meals. This is ridiculous. They should be given one hour before a meal or midway between feedings. In that way you cut down the level of acidity and you have a lower peak before the next meal. Never give antacids immediately after food when you've already got its effect cutting the acidity in the stomach. I prefer a mixture of antacids—calcium carbonate, sodium bicarbonate, and magnesium oxide. I think that's better than just a single one. But the time is the important factor."

—F. AVERY JONES, M.D., London

Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Pesticide Illness is Now Reportable

A NEW LAW REQUIRES that physicians report cases of pesticide poisoning and related conditions to their local health officers. Chapter 9, Division 3, Section 2950 of the California Health and Safety Code reads:

"Any physician and surgeon who knows, or has reasonable cause to believe, that a patient is suffering from pesticide poisoning or any disease or condition caused by a pesticide shall promptly report such fact to the local health officer. Each local health officer shall report to the county agricultural commissioner, the Director of Agriculture, and the State Director of Public Health, on a form prescribed by the State Director of Public Health, each case reported to him pursuant to this section within seven days after receipt of any such report."

Pesticides are defined as "substances or mixtures of substances intended to be used for controlling, preventing, destroying, repelling, or mitigating any pest. The term includes insecticides, fungicides, rodenticides, herbicides, defoliants, plant growth regulators, pre-harvest desiccants, wood-preserveds, anti-fouling and mildew-controlling paints, as well as substances for control of snails, predatory animals, algae, and other undesirable forms of plant and animal life."

Where there is an urgent public health hazard, the physician should immediately telephone the

local health officer. Such an emergency might be indicated in the case of several farm workers with suspected organophosphate poisoning apparently contracted on the job, where other workers are likely to be exposed, or multiple cases among non-agricultural workers or the general public. Other cases such as individual instances of poisoning need not be reported by telephone.

In all cases, including those reported immediately by telephone, the physician is required to send a written report within two days. A brief report form on a fold-over postcard is available at the local health department or the State Department of Public Health. The latter will send such forms directly to those physicians who are known to see occupational cases of pesticide poisoning frequently.

Where the type of pesticide involved is unknown, the physician may ask the county agriculture commissioner for chemical identification information necessary to institute treatment. The commissioner has complete records of spray in all agricultural areas in the county. In cases of non-agricultural poisoning the physician may wish to contact the closest poison control center regarding ingredients.

Reports to the local health officer do not relieve the physician of responsibility to report cases of occupational illness on the Doctor's First Report of Work Injury, as required by the Labor Code, Section 6407.

Pesticide poisoning is an increasing hazard today. Accidents result from improper handling or mishaps in transportation and storage of pesticides, as well as from agricultural and occupational exposure. Four outbreaks of organophosphate poisoning from foliage residues, involving more than 50 farm workers, occurred in California in 1970.

The doctor's report will be the first in a series

of steps designed to help reduce pesticide poisoning. The reports will serve as an early warning of pesticide outbreaks to the county agricultural commissioners, the State Department of Public Health, and the State Department of Agriculture, enabling the appropriate agency or agencies to investigate unsafe foliage residues before other workers are poisoned or to remove workers from sprayed areas. They will also provide information of adverse reactions to new or older products among the general population. In some instances, physicians' reports may point to large-scale public health hazards, such as pesticide pollution of waters, unsafe disposal of materials or containers

where children might get at them, or contamination of articles in transport.

The State Department of Public Health, among other agencies, conducts surveillance and epidemiological studies on acute pesticide poisoning. Physicians' reports will help the Department to develop statistics and assess the level of pesticide-related illness among all segments of the population, presently unknown except for cases reported as occupational.

The Department will supply, on request, a technical bulletin for physicians entitled "Diagnosis and Treatment of Phosphate Ester Pesticide Poisoning."

## MEMBERSHIP OF COMPONENT SOCIETIES OF THE CALIFORNIA MEDICAL ASSOCIATION

Following is a list of the numbers of members of each component society of the California Medical Association as of September 1, 1970:

Alameda-Contra Costa . . . . .	1,974	Sacramento . . . . .	729
Butte-Glenn . . . . .	123	San Benito . . . . .	9
Forty First . . . . .	114	San Bernardino . . . . .	560
Fresno . . . . .	431	San Diego . . . . .	1,424
Humboldt-Del Norte . . . . .	103	San Francisco . . . . .	1,950
Imperial . . . . .	47	San Joaquin . . . . .	320
Inyo-Mono . . . . .	21	San Luis Obispo . . . . .	108
Kern . . . . .	268	San Mateo . . . . .	639
Kings . . . . .	27	Santa Barbara . . . . .	368
Lassen-Plumas-Modoc-Sierra . . . . .	25	Santa Clara . . . . .	1,311
Los Angeles . . . . .	9,062	Santa Cruz . . . . .	157
Marin . . . . .	272	Shasta-Trinity . . . . .	99
Mendocino-Lake . . . . .	65	Siskiyou . . . . .	20
Merced . . . . .	80	Solano . . . . .	100
Monterey . . . . .	238	Sonoma . . . . .	229
Napa . . . . .	107	Stanislaus . . . . .	208
Orange . . . . .	1,392	Tehama . . . . .	17
Placer-Nevada . . . . .	104	Tulare . . . . .	138
Riverside . . . . .	411	Ventura . . . . .	300
		Yolo . . . . .	95
		Yuba-Sutter-Colusa . . . . .	74
		Total . . . . .	23,719



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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AINLAY, GEORGE WILLIAM, Santa Monica. Died September 24, 1970 in Santa Monica of coronary artery disease, aged 73. Graduate of University of Nebraska College of Medicine, Omaha, 1927. Licensed in California in 1943. Doctor Ainlay was a member of the Los Angeles County Medical Association.

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BEERS, SHERMAN JOHNSON, San Francisco. Died December 15, 1970 near San Francisco, aged 64. Graduate of Yale University School of Medicine, New Haven, 1932. Licensed in California in 1949. Doctor Beers was a member of the San Francisco Medical Society.

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BONES, WILLIAM EDWARD, El Segundo. Died November 29, 1970 in Pacific Palisades of heart disease, aged 64. Graduate of Vanderbilt University School of Medicine, Nashville, 1931. Licensed in California in 1941. Doctor Bones was a member of the Los Angeles County Medical Association.

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CARLSON, EDWARD F., SR., Oakland. Died December 19, 1970 in Oakland of heart disease, aged 64. Graduate of Washington University School of Medicine, St. Louis, 1933. Licensed in California in 1934. Doctor Carlson was a member of the Alameda-Contra Costa Medical Association.

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CASSELS, WILLIAM HENDERSON, San Mateo. Died November 24, 1970 in San Mateo of heart disease, aged 69. Graduate of University of Alberta Faculty of Medicine, Edmonton, 1962. Licensed in California in 1963. Doctor Cassels was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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CORBIN, EDWARD, Northridge. Died December 5, 1970 of malignant melanoma, aged 67. Graduate of Georgetown University School of Medicine, Washington, D.C., 1929. Licensed in California in 1959. Doctor Corbin was a member of the Los Angeles County Medical Association.

MOORE, ALOIS E., San Diego. Died December 4, 1970 in San Diego, aged 63. Graduate of Tulane University School of Medicine, New Orleans, 1931. Licensed in California in 1938. Doctor Moore was a member of the San Diego County Medical Society.

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NESCHE, GEORGE ELWOOD, Oakland. Died November 28, 1970 in Oakland of myocardial infarction, aged 69. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1929. Doctor Nesche was a member of the Alameda-Contra Costa Medical Association.

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\*

O'CONNOR, JOHN JAY, Scottsdale, Ariz., formerly San Francisco. Died December 9, 1970 in Phoenix, aged 73. Graduate of St. Louis University School of Medicine, 1926. Licensed in California in 1926. Doctor O'Connor was a member of the San Francisco Medical Society.

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\*

REES, DEE M., Monterey Park. Died December 4, 1970, aged 69, in Palm Springs of injuries when beaten by an intruder. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Doctor Rees was a member of the Los Angeles County Medical Association.

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\*

SANTAMARIA, ANDRES, Los Angeles. Died October 13, 1970 in Monterey Park of lymphogranuloma, aged 54. Graduate of Universidad Nacional Facultad de Medicina, Mexico, D.F., 1940. Licensed in California in 1955. Doctor Santamaria was a member of the Los Angeles County Medical Association.

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SCHELL, JOSEPH PERRY, San Jose. Died December 20, 1970 in San Jose, aged 90. Graduate of University of Nashville, Medical Department, 1909. Licensed in California in 1919. Doctor Schell was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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TUCKER, MARSHALL BOYD, Oakland. Died November 26, 1970 in Oakland of arteriosclerotic heart disease, aged 61. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1934. Licensed in California in 1935. Doctor Tucker was a member of the Alameda-Contra Costa Medical Association.

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**CALIFORNIA MEDICAL ASSOCIATION • MARCH 13-17, 1971**

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**HOUSE OF DELEGATES OPENING SESSION, ANAHEIM CONVENTION CENTER, SATURDAY AFTERNOON, MARCH 13**

1. Fill in the form below *completely* for room accommodations at the CMA's 1971 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, except for suites, must be made through the Disneyland Hotel, 1441 S. West Street, Anaheim, California 92802, by February 12, 1971.
4. ALL SUITE RESERVATIONS MUST BE CLEARED THROUGH THE CMA CONVENTION OFFICE, SAN FRANCISCO. IF YOU ARE REQUESTING A SUITE, DIRECT YOUR REQUESTS TO: CMA CONVENTION OFFICE, 693 SUTTER STREET, SAN FRANCISCO, CA 94102.
5. CANCELLATIONS: Please notify Disneyland Hotel, 1441 S. West Street, Anaheim, of all cancellations.  
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THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

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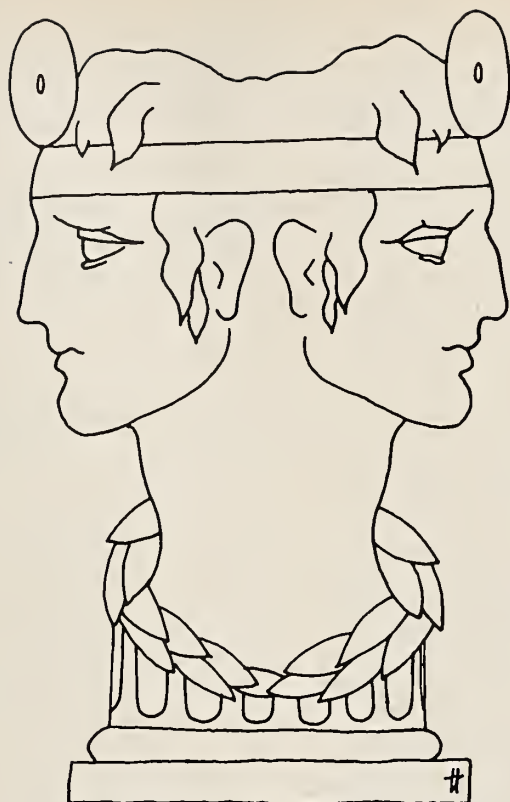
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March 13-17, 1971



# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(Formerly WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a National Institutes of Health grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ALCOHOLISM AND DRUG USE

March 13-14—**Drug Dependence.** See Of Interest to All Physicians, March 13-14.

## CANCER

April 13—**Annual Cancer Conference.** San Diego County Medical Society, San Diego County Branch-American Cancer Society and US Naval Hospital, San Diego at US Naval Hospital, San Diego. Tuesday. Contact: Sidney L. Saltzstein, M.D., Dept. of Pathology, Surgical Pathology Service, University Hospital of San Diego County, 225 W. Dickinson St., San Diego 92103. (714) 291-3330.

Continuously—**Tumor Board—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 2-3 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## MEDICINE

February 17-19—**Medical Complications in Pregnancy.** See Ob-Gyn, February 17-19.

February 19-20—**American College of Physicians—Southern California Regional Meeting.** El Mirador Hotel, Palm Springs. Friday-Saturday. Contact: Edward E. Boland, M.D., Governor for Southern California, ACP, 321 N. Larchmont Blvd., Los Angeles 90004. (213) 462-1281.

February 20—**Intensive Medical Care Symposium.** STAN. Saturday. Shock, thromboembolism, tachyrrhythmias, respiratory failure, bleeding disorders, disseminated intravascular coagulation and fibrinolysis, drug injection, hazards of intensive care.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California, San Francisco Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

February 24-25—**Critical Care Medicine and Circulatory Shock.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. \$65.

February 24-26—**7th Annual Course on the Evaluation of Pulmonary Function.** Tuberculosis and Respiratory Disease Association of California at Town and Country Inn, Mission Valley, San Diego. Wednesday-Friday. \$100 members of American Thoracic Society, \$125 others. 24 hrs. Contact: Miss Louise Ratcliff, TARDAC, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

February 25-27—**Pediatric Nephrology.** See Pediatrics, February 25-27.

February 26-27—**The Office Care of Dermatologic Disorders.** STAN. Friday-Saturday. Keynote lectures on psoriasis, contact dermatitis, diabetic problems of the foot. \$60. 11 hrs.

February 27—**Advances in Diagnosis and Treatment of Angina Pectoris.** PMC. Saturday. 8 hrs.

February 28—**Hypertension—Fifth Annual Leon Wolpe Memorial Lecture.** Hollywood Community Hospital at Sheraton-Universal Hotel, Universal City. Sunday. Contact: William Grasske, M.D., Hollywood Community Hospital, 6245 De Longpre Ave., Hollywood 90028. (213) 462-2271.

March 1-12—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Anrum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

March 1-19—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

March 4-6—**Intensive Care Unit: A Team Approach.** PMC. Thursday-Friday.

March 4-6—**Treatment of Neonatal Pulmonary Disease.** See Pediatrics, March 4-6.

March 5—**Invasive and Non-Invasive Techniques in the Evaluation of Myocardial Function.** USC at Hilton Hotel, Pasadena. Friday. \$35.

March 6—**Lipid Disorders or the Great Fat Controversy.** UCSF. Saturday. Designed for the clinician and nutritionist. Electrophoretic techniques; occurrence, identification and prognosis, current nutritional and pharmacologic means of control of lipid disorders. \$15. 5½ hrs.

March 7-12—**Arrhythmia Retreat.** USC at Erawan Garden Hotel, Indian Wells. Sunday-Friday. \$200.

March 11-13—**Neurology: Recent Advances.** UCSF. Thursday-Saturday.

March 12—**Electromyography Symposium.** USC. Friday.

March 13—**Recognition of Levels of Unconsciousness in the Comatose Patient.** PMC. Saturday.

March 13-14—**Antibody Identification: Problem Cases.** UCSF at Irwin Blood Bank, San Francisco. Saturday-Sunday.

March 14-17—**Current Topics in Gastrointestinal Disease.** UCLA at El Mirador Hotel, Palm Springs. Sunday-Wednesday. \$125.

March 14-18—**American College of Allergists—Annual Meeting and Pre-Congress Seminar.** Fairmont Hotel, San Francisco. Sunday-Thursday. \$10 nonmembers. Contact: Eloi Bauers, Exec. Vice-Pres., ACA, 2100 Dain Tower, Minneapolis 55402. (612) 332-2948.

March 15-19—**Transfusion Tests and Immunohematology Tutorial.** American Society of Clinical Pathologists and Memorial Hospital of Long Beach at Memorial Hospital of Long Beach, Long Beach. Monday-Friday. ABO grouping, Rh testing, compatibility tests, antibody identification, hemolytic disease of the newborn, transfusion reaction investigation, quality control, records, component therapy. \$150. 40 hrs. Contact: Miss Peg Driscoll, Staff Assistant, ASCP, 710 Wolcott Ave., Chicago 60612. (212) 783-1336.

March 19-21—**New Perspectives in Diagnosis and Management of Myocardial Infarction—1971.** American College of Cardiology and Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Friday-Sunday. \$100 members, \$125 others. Contact: Miss Mary Anne McInerny, Dir., Dept. of Continuing Education Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

March 27—**Auscultation of the Heart.** PMC. Saturday.

April 3—**Postgraduate Symposium in Infectious Diseases.** STAN. Saturday. Recent developments in pathogenesis, diagnosis and management of patients with infection.

April 7—**Neurology for the Internist.** LLU. Wednesday. \$25. 8 hrs.

April 17-18—**Pathophysiology of Aging.** PMC. Saturday-Sunday.

April 19-21—**Cardiology for the Consultant.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Monday-Wednesday. Contact: Miss Mary Anne McInerny, Dir., Dept. of Continuing Education Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

April 22—**Fourteenth Annual Physicians Symposium—Workshop on Arrhythmias and Heart Failure.** Santa Clara County Heart Association at San Jose Hyatt House, San Jose. Thursday. \$20. 6 hrs. Contact: William G. Allayaud, Exec. Dir., SCCCHA, 1984 The Alameda, San Jose 95126. (408) 248-1517.



April 22-24—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 23-24—**Second Annual Cardiac Care Symposium.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday-Saturday. \$35. Contact: Miss Marilyn Woods, OCHA, 1043 Civic Center Drive West, Santa Ana 92703. (714) 547-3001.

May 3-14—**Coronary Care Unit Program for Physicians.** See Medicine, March 1-12.

May 3-21—**Coronary Care for Physicians Training Program.** See Medicine, March 1-19.

May 13-16—**California Heart Association—Annual Meeting Scientific Sessions.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: Rodman Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.

Continuously—**Coronary Care.** St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—**Coronary Care Unit Training for Physicians.** CRMP Area VI and San Bernardino County General Hospital at San Bernardino County General Hospital. Four week courses at monthly intervals, scheduled by arrangement. For practicing physicians working in and directing CCU's. Bedside care, electrocardiography, physical diagnosis, clinical history, therapy, insertion of pacemakers, cardioversion. 160 hrs. Contact: Carl L. Cook, Jr., M.D., San Bernardino County General Hospital, 780 E. Gilbert St., San Bernardino 92404. (714) 885-3411.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSPB, 4200 California St., San Francisco 94118. (415) 387-0934.

Continuously—**Medico-Surgical Cardiovascular Seminar.** STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

Continuously—**Cardiology Conferences—CRMP Area III.** Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

## Grand Rounds—Medicine

### Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

### Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

### Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

## Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## OBSTETRICS AND GYNECOLOGY

February 17-19—**Medical Complications in Pregnancy.** USC and the American College of Physicians at USC. Wednesday-Friday. Cardiovascular disease, hypertension, diabetes and anemia occurring in pregnancy. Contact: USC. \$80 ACP members, \$125 others. 17 hrs.

March 6—**Therapeutic Abortion.** PMC. Saturday.

March 24—**Urological Disorders in Women.** LLU. Wednesday. \$25. 8 hrs.

May 3-7—**American College of Obstetricians and Gynecologists—Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. Contact: Michael Newton, M.D., Dir., ACOG, 79 W. Monroe St., Chicago 60603. (312) 236-6814.

May 12—**Problems in Reproduction.** LLU. Tuesday. \$25. 8 hrs.

## Grand Rounds—Obstetrics and Gynecology

### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

11:30 a.m., First Floor Auditorium, Room I3-I05, UCLA Medical Center. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

### Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

### Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

## Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

## PEDIATRICS

February 20-21—**Psychiatric Evaluation of the Child.** See Psychiatry, February 20-21.

February 23-25—**Conference on Hearing Screening on the Newborn.** Maternal and Child Service of HEW and Bureau of Maternal and Child Health, State Department of Public Health. Hilton Inn, San Francisco International Airport. Tuesday-Thursday. 16 hrs. Contact: Edith Krabach, Bureau of Maternal and Child Health, State Department of Public Health, 2151 Berkeley Way, Berkeley 94704. (415) 843-7900.

February 25-27—**Pediatric Nephrology.** UCSF. Thursday-Saturday. Parental/fluid therapy, saline and effective extracellular fluid volume, acid base data, diuretics, acute renal failure, chronic uremia in children, divalent cation metabolism and parathormonic function in uremic children, hypertension, glomerulus, tubular control of acid-base, diseases of tubular dysfunction, urologic basis of recurrent urinary tract infection and bacteriology. Sections: body composition, glomerular diseases, tubular dysfunction, urologic problems. 13½ hrs.

February 26-28—**Second Annual Southern California Pediatric Postgraduate Course.** American Academy of Pediatrics, Chapter II, District IX; Childrens Hospital of Orange County; Los Angeles Pediatric Society; Southwestern Pediatric Society; and Childrens Hospital of Los Angeles at El Mirador Hotel, Palm Springs. Friday-Sunday. Practical Office Pediatrics. \$50. 15 hrs. Contact: Neil N. Litman, M.D., Program Chairman, 5830 Overhill Drive, Los Angeles 90043. (213) 291-1161.

March 4-6—**Treatment of Pulmonary Disease in Neonates.** UCI and CRMP Area VIII at Childrens Hospital of Orange County, Orange. Thursday-Saturday. Contact: Bruce D. Ackerman, M.D., Pediatric Pulmonary Demonstration Center, Dept. of Pediatrics, UCI.

April 24—**Pediatric Otolaryngology.** PMC. Saturday.

May 13-15—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

## Grand Rounds—Pediatrics

### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.



## Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

## Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

## Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

## PSYCHIATRY

February 15—**Psychodrama**. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Mondays through March 22. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

February 20-21—**Psychiatric Evaluation of the Child**. UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

February 23—**Clinical Psychiatry**. UCLA. Tuesdays through May 11.

February 26-28—**Hypnosis: Therapy and Practice**. UCLA and American Society of Clinical Hypnosis, Education & Research Foundation. Friday-Sunday.

March 1—**Sex: Past, Present, and Future**. UCSF. Monday evenings through April 5.

March 10—**Sex and Society in the Seventies**. LLU. Wednesday. \$25. 8 hrs.

March 12-13—**Suicide: Causes and Prevention**. University of California Extension, Riverside at Sproul Hall, Riverside. Friday-Saturday. \$26. 9 hrs. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

April 2—**Introduction to Child Psychiatry**. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Fridays through June 4. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

April 6.—**Schools of Psychiatric Thought**. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Tuesdays through June 22. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

April 7—**Group Methods**. UCSF at V A Hospital, San Francisco. Wednesdays through June 9. \$30 full program, \$20 lectures only, \$2 individual lectures. 15 hrs.

May 1—**Group Process**. UCSF at Modesto State Hospital, Modesto. Saturday.

## Grand Rounds—Psychiatry

### Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

## RADIOLOGY—PATHOLOGY

March 8-12—**Diagnostic Radiology**. UCSF. Monday-Friday. For radiologists in clinical practice. Urinary, Pulmonary, Gastrointestinal, Pediatric Radiology. \$125. 25 hrs.

April 10—**Scintillation Camera Workshop**. UCSF. Saturday.

April 30-May 1—**Radiology of the Liver, Biliary Tract and Pancreas—Fourth Annual Leo G. Rigler Radiology Symposium**. UCLA. Friday-Saturday.

Continuously—**UCSF Radiology Rounds, Seminars, and Conferences**. Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiology Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.

Continuously—**Principles and Clinical Uses of Radioisotopes**. UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

## Grand Rounds—Radiology-Pathology

### Mondays

Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

### Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

## SURGERY—ANESTHESIOLOGY

February 26-27—**Retinal Surgery**. UCSF. Friday-Saturday. \$125. 13½ hrs.

March 5-6—American Society for Surgery of the Hand. Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Lee Milford, M.D., 869 Madison Avenue, Memphis, Tenn. 38104.

March 6-11—American Academy of Orthopedic Surgeons. Civic Auditorium, San Francisco. Saturday-Thursday. Contact: John K. Hart, Exec. Sec., AAOS, 430 N. Michigan Ave., Chicago 60611. (312) 822-0970.

March 10-14—Controversial Areas in Surgery. UCLA at El Mirador Hotel, Palm Springs. Wednesday-Sunday. \$150.

March 20—Emergency Room Techniques. PMC. Saturday. 8 hrs.

March 24—Urological Disorders in Women. See Ob/Gyn, March 24.

April 1-2—General Surgery. UCSF. Thursday-Friday.

April 2-3—Proctology. UCSF. Friday-Saturday.

April 17-18—Vascular Surgery. USC at Hilton Hotel, Los Angeles. Saturday-Sunday.

April 17-18—Sixteenth Annual Postgraduate Assembly—Los Angeles Society of Anesthesiologists. Hilton Hotel, Los Angeles. Saturday-Sunday.

April 19-21—Glaucoma Conference. UCSF at St. Francis Hotel, San Francisco. Monday-Wednesday. \$25.

April 24—Pediatric Otolaryngology. See Pediatrics, April 24.

April 24—Application of Casts, Splints and Bandages. UCLA. Saturday.

May 1—Orthopedic Problems. UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

May 2-7—Biennial Western Conference on Anesthesiology. Princess Kaiulani Hotel, Honolulu. Sunday-Friday. \$100. Contact: Eldon E. Smith, M.D., 2270 Kalahua Ave., Suite 1708, Honolulu 96814.

May 8—Audiology. PMC. Saturday.

#### Grand Rounds—Surgery

##### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

##### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

##### Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

##### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

##### Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

#### OF INTEREST TO ALL PHYSICIANS

February 19-25—Loma Linda Postgraduate Assembly. LLU Alumni Association at LLU and Ambassador Hotel, Los Angeles. Friday-Thursday. Cardiology, Ophthalmology, Dermatology, Pediatrics, Internal Medicine, Surgery, Neurology, Radiology, Business, Orthopedics, Plastic Surgery and Inhalation Therapy. \$50. 15 hrs. Contact: Paul H. Deeb, M.D., General Chairman, 1832 Michigan Ave., Los Angeles 90033. (213) 262-2173.

February 22-24—San Diego Biomedical Symposium—1971. UCSD at Ramada Inn, Harbor Island, San Diego. Monday-Wednesday. Information processing and Instrumentation, New Developments from Industry Applicable to Hospital Environment, Data Storage and Retrieval, Instrumentation for Care of the Acutely Ill, Microprogrammed Minicomputers, Signal Conditioning and Preprocessing, Biomedical Applications of Simulation Techniques. Contact: R. D. Yoder, Dept. of Community Medicine, UCSD School of Medicine, University Hospital of San Diego County, 225 W. Dickinson St., San Diego 92103. (714) 291-3330.

March 7—Personal Adjustments and Human Relations: Communication and Ethics: A Symposium for Medical Assistants. UCSF. Sunday.

March 12-19—Marquette Medical Alumni Association. Maui Hilton Hotel, Maui, Hawaii. One week. Contact: Robert H. Herzog, Marquette Medical Alumni Association, 561 N. 15th St., Milwaukee 53233.

March 13-14—Drug Dependence. UCSF at Napa State Hospital, Imola. Saturday-Sunday. Pharmacological basis, social and psychiatric determinants, the drug scene, panel discussions. \$15. 5 hrs.

March 13-17—California Medical Association—Annual Meeting. Disneyland Hotel, Anaheim. Saturday-Wednesday. Psychiatric Focus on Medical and Social Change, Environmental Activism—A Positive Approach, Continuing Medical Education—Voluntary or Involuntary?



March 18-21—**Association for the Advancement of Medical Instrumentation.** International Hotel, Los Angeles. Thursday-Sunday. Contact: Michael J. Miller, AAMI, 9650 Rockville Pike, Bethesda, Md. 20014.

April 12—**Medical Centers of the Orient.** USC on tour in Japan, Taiwan, Thailand, Singapore, Malaysia and Hong Kong. One month through May 12.

April 17-18—**Kern Postgraduate Conference.** Kern County Medical Society at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: Milton L. Smale, M.D., Chairman, 1930 Eighteenth St., Bakersfield 93301. (805) 327-7637.

April 21-22—**Eighth Annual Spring Symposium for Physicians Practicing General Medicine.** Los Angeles County Heart Association and Los Angeles County Academy of General Practice at Ambassador Hotel, Los Angeles. Wednesday-Thursday. 10 hrs. Contact: Joyce Martin, Program Associate, LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

April 27-May 1—**Hawaii Medical Association Annual Meeting.** Ilikai Hotel, Honolulu. Thursday-Saturday. Contact: H. Tom Thorson, Acting Exec. Dir., HMA, 510 S. Beretania St., Honolulu 96813. (808) 536-7702.

April 28-May 1—**American College Health Association.** Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: James W. Dilley, Exec. Sec., ACHA, 2807 Central St., Evanston, Ill. 60201. (312) 491-9775.

May 1—**Facial Pain.** PMC. Saturday.

May 7-8—**Trauma.** UCSF. Friday-Saturday.

May 8—**Utilization Review in Hospitalized Patients.** UCSF at St. Francis Hotel, San Francisco. Saturday.

May 8—**Second Annual Clinical Pharmacology Symposium: Current Concepts in Drug Therapy for the Practicing Physician.** STAN and Palo Alto Medical Clinic at Palo Alto Medical Clinic, Palo Alto. Saturday. \$15.

#### CMA Postgraduate Institutes and Circuit Courses

February 15, 16, 17—March 8, 9, 10—**Annual Postgraduate Circuit Courses—Spring Session.** CMA and UCD at Mt. Shasta Community Hospital, Mt. Shasta; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn. \$20 for Spring Session. Contact: CMA.

March 4-5—**West Coast Counties Regional Postgraduate Institute.** CMA, UCSF and Monterey County Medical Society at Del Monte Lodge, Pebble Beach. Thursday-Friday. \$20. Contact: CMA.

April 30-May 1—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA, UCLA and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. \$20. Contact: CMA.

May 14-15—**Redwood Regional Postgraduate Institute.** CMA, STAN and Humboldt-Del Norte County Medical Society at Eureka Inn, Eureka. Friday-Saturday. \$20. Contact: CMA.

May 14-15—**Medical Photography.** UCSF. Friday-Saturday.

Continuously—**Basic Science Correlation in Disease.** VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.

Continuously—**Ventura General Hospital Program.** UCI and Ventura General Hospital at Ventura General Hospital, Ventura. Monthly lectures by UCI faculty. January 16, Indications for Thyroid Surgery. Contact: UCI.

Continuously—**Postgraduate Medical Lecture Series—Orange County.** UCI and Orange County Chapter, American Academy of General Practice at Saddleback Inn, Santa Ana. Monthly lectures by UCI faculty. March 8, The Hyperactive Child; April 12, Orthopedic Examination of Hips and Feet in Infants and Children; May 10, Manipulative Bodily Therapy. Contact: UCI.

Continuously—**Postgraduate Medical Lecture Series—Riverside-San Bernardino.** UCI and Riverside-San Bernardino Chapter, American Academy of General Practice at Rams Horn Inn, San Bernardino. Monthly lectures by UCI faculty. February 18, Facts and Fantasies of Sensitivity Training; March 18, Current Concepts and Management of Hepatitis; April 15, General Plastic and Reconstructive Surgery. Contact: UCI.

Continuously—**Inter-Hospital Conference.** UCSD and participating hospitals in the San Diego area at Radiology main conference room, UCSD. Weekly conferences conducted by various hospitals. Consult UCSD for dates and participating hospitals.

Continuously—**Weekly Seminar for Graduate Students.** UCSD at Basic Sciences Building, UCSD. Weekly Wednesday seminars, open to interested physicians. 12 noon.

Continuously—**Dean's Day Program.** UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. February 25, Pathology; March 25, Radiology; April 22, Community Medicine. Contact: UCSD.

Continuously—**Biomedical Lecture Series.** UCSD. March 17, April 21, 8:00 p.m., Basic Sciences Building, UCSD.

Continuously—**Basic Science Lecture Series.** UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

Continuously—**Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malpractice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MMN Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all California medical schools. Contact: Richard R. Getz, Exec. Dir., MMN, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

Continuously—**Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Practicing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Endocrinology-Metabolism, Gastroenterology, Hematology, Neurology,

Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: February-March, April-May. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, environmental radiation standards and nuclear power plants, overpopulation, abortion and contraception, technological problems of power generation in the United States, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and supersonic transport. Contact: John W. Farquhar, M.D., Assoc. Prof. of Medicine, STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

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# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**TEXTBOOK OF IMMUNOPATHOLOGY—Volumes I and II—**Peter A. Miescher, Professor of Hematology; Head, Division of Hematology, Hôpital Cantonal, University of Geneva, Geneva, Switzerland; and Hans J. Muller-Eberhard, M.D., Member Scripps Clinic and Research Foundation, Department of Experimental Pathology, La Jolla, California, and Professor of Pathology in Residence, University of California at San Diego, La Jolla, California; with 75 contributors. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. Volume I, 384 pages, \$19.75. Volume II, 420 pages, \$24.75.

For anyone interested in immunopathology, and few of us can afford not to be, these two volumes will be of great interest. They start with a section on general immunopathology in which the factors important in immunopathology are discussed followed by chapters on pathogenic immune reactions and experimental immune diseases. The section on general immunopathology concludes with chapters on the action of drugs on immune phenomena. The second part of the book deals with clinical immunopathology and here a great variety of diseases which may be of immune origin are discussed.

Inevitably in a book written by many authors there is some unevenness in coverage. Also some chapters were finalized in 1966 while others include references up to 1968. As a result, some of the more recent findings in certain rapidly advancing fields could not be included. Nevertheless, this book will provide an excellent rapid desk reference to the field and anyone contemplating work in this area will find it an excellent starting point.

B. H. RUEBNER, M.D.

**UROLOGY—Vol. 1-3—3rd. Ed.**—Edited by Meredith F. Campbell, M.S., M.D., Late Professor of Urology, New York University, and Consulting Urologist, Bellevue Hospital, New York; and J. Hartwell Harrison, M.D., Cutler Professor of Surgery (Urology), Harvard Medical School, and Chief of Urology, Peter Bent Brigham Hospital, Boston; with the collaboration of seventy-four contributing authorities. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1970. 3,046 pages, \$110.00 per set.

Brought up to date in its third edition, this textbook maintains a unique position as the most comprehensive and authoritative compendium on all aspects of urology that is available in the English language. Readers acquainted with the previous edition will welcome several new chapters on aspects of urology which have achieved prominence in recent years. Thus a chapter by D. R. Smith on the "Pathophysiology of Vesicoureteral Reflux" presents an admirable and balanced review of the subject, complementing the previous chapters on pediatric urology by Dr. Campbell. The vagaries of the physiology of micturition and bladder innervation are admirably presented by Boyarsky and Ruskin. The advances in diagnostic radioisotopes are properly accorded a separate chapter by C. C. Winter which should bring up to date old and new urologists alike. The section on Urologic

Surgery in the third volume contains a welcome new chapter on renal transplantation by W. E. Goodwin and D. C. Martin which is to be commended for the use of the outstanding illustrations previously published by the Starzl group. Some of the other chapters on surgical technique show little change and, while quite adequate, do suffer by comparison with the completely new presentations in the recently published volume *Urologic Surgery* edited by J. F. Glenn and W. H. Boyce.

Some duplication is unavoidable in the overlapping contributions from various authorities, perhaps even desirable. Old feathers molt slowly, however, and some of them ruffle the otherwise smooth presentation of this edition. In that category must be included the chapters on "Care of Urological Patient Before and After Operation" and "Urologic Endocrinology." Overall, however, this three-volume text remains indispensable to the urologist and to every medical library.

R. F. GITES, M.D.

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**OCCUPATIONAL CONTACT DERMATITIS**—Robert M. Adams, M.D., Palo Alto Medical Clinic, Palo Alto; Clinical Assistant Professor, Department of Dermatology, Stanford University School of Medicine, Stanford. J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa. (19105), 1969. 262 pages. \$16.50

This practical, well-done text by a Palo Alto dermatologist encompasses the number one cause of job-related disease. Contact dermatitis, either from direct irritation (80%) or allergic sensitization (20%), results in tremendous economic loss and over 800,000 compensation cases each year. Disability and discomfort may be severe, and the attending physician is often hard-pressed to correctly diagnose and relieve the problem.

This book should greatly aid the practicing physician, whether dermatologist, general practitioner, or industrial specialist. Based on wide personal experience and thorough literature review, it simplifies such things as occupational history-taking and the diagnosis and treatment of dermatitis. Specific instruction is given for cutaneous patch testing, a simple diagnostic tool for testing suspected allergens and photosensitizing chemicals. Thirty easily obtained substances are suggested for the initial patch testing of industrial patients.

Encyclopedic lists of allergens which are encountered in commercial products, industrial ingredients, and 100 occupations make detective work easier. The lists serve as excellent references, along with extensive chapter bibliographies. Special chapters discuss the most common industrial offenders, including soaps, solvents, resins, metals and petroleum derivatives.

Several chapters are unique and should particularly interest lawyers, industrial workers, and insurance experts. Plant survey and inspection is described and highly rec-



ommended for familiarization with the industrial environment. Methods of dermatitis prevention are suggested, including cartoon campaigns urging the use of protective clothing, improved hygiene, and barrier creams. Workmen's compensation laws and hearings are reviewed with special attention to the problems of sensitization and the aggravation and recurrence of dermatitis.

This book belongs in the office of every physician involved in treating contact dermatitis. Every dermatology library should also have a copy.

DORINDA LOEFFEL, M.D.

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**DISEASES OF BONE AND JOINTS**—Louis Lichtenstein, M.D., Clinical Professor of Pathology, University of California, San Francisco; Professor Extraordinario, National University of Mexico; Honorary Member, Spanish Orthopedic Society (SECOT). The C. V. Mosby Company, 3207 Washington Boulevard, Saint Louis (63103), 1970. 228 pages, 287 illustrations, \$17.50.

The author presents in a concise, easily read and understandable way basic concepts of diseases of bones and joints. It discusses in a succinct way available pertinent information relative to physiologic, genetic, immunologic and biochemical data and further integrates this at every opportunity with clinical and pathologic findings.

No attempt has been made to present an exhaustive discussion of any one condition but the coverage is quite adequate for routine clinical needs in differential diagnosis and prognosis. The author of necessity makes no effort to discuss treatment of the multiple lesions he describes but does, in certain instances, point out acceptable therapy measures. Further, there is included an excellent bibliography with references to specific articles and books for any one interested in pursuing a more complete review and study of any particular condition.

Illustrations (287) both radiographic and microscopic with a few of gross pathology are excellent. Perhaps no work ever has enough illustrations but again the author is not attempting to completely cover any one subject.

Thus, this book contributes well many salient points to the overall subject of diseases of bones and joints. It is recommended for study by orthopaedists, radiologists, internists, pediatricians and any interested in, or whose practice in part or all, embraces this important field of medicine.

PAUL E. McMASTER, M.D.

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**EMERGENCY TREATMENT AND MANAGEMENT**—Fourth Edition—Thomas Flint, Jr., M.D., Formerly Senior Consultant, Emergency Department and Director, Division of Industrial Relations, Permanente Medical Group and Kaiser Foundation Hospitals, Oakland, Richmond and Vallejo, Ca.; and Harvey D. Cain, M.D., Chief of Industrial Medicine and Rehabilitation, Permanente Medical Group and Kaiser Foundation Hospital, Sacramento. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 733 pages, \$11.50.

This represents the fourth edition of a manual written for the physician engaged in emergency care as a guide to "portal to portal care in emergency situations." It is divided into three major sections: general principles, treatment of specific conditions, and administrative, clerical and medicolegal procedures. It is thoroughly indexed and extensively cross referenced, but contains no bibliography. A separate section (printed on blue paper to offset it from the rest of the text) deals with the treatment of acute poisoning. The writing is lucid with a minimal, but sometimes inadequate, number of pictorial guides and diagrams. Brevity and clarity characterize the main body of the text.

The authors' very brief treatment of a diverse and extensive area of medical care is perhaps the most obvious

advantage and disadvantage of this text. While the practicality and efficiency of this handbook are evident, the lack of clear explanations for various therapeutic maneuvers and the absence of a bibliography are significant disadvantages for the physician interested in learning the rationale for his treatment. This disadvantage is underscored when incomplete recommendations are recorded, i.e., . . . "antibiotics should be administered." The readers' immediate reaction is which antibiotics and for what organisms. Nevertheless, as a quick guide to therapy in the emergency situation it is a useful addition.

A unique and quite useful aspect of the text is the section dealing with administrative, clerical and medicolegal principle. Rarely covered in other books of this sort, it offers some very practical suggestions for dealing with these non-clinical matters. The pictures of actual forms used in these matters will also be of definite assistance to the emergency physician.

Overall this is a handy, practical therapeutic guide for emergency treatment, but one which falls short in its thoroughness and its ability to stimulate rational understanding of specific therapeutic measures.

HIBBARD E. WILLIAMS, M.D.

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**OSTEOPOROSIS**—Edited by Uriel S. Barzel, M.D., Montefiore Hospital and Medical Center, Bronx, New York. Grune and Stratton, Inc., 737 Third Avenue, New York, N.Y. (10017), 1970. 290 pages, \$25.00.

This thin volume contains 21 edited essays and brief discussion by a group of experts assembled at Montefiore Hospital in New York, June 25-26, 1969. Most chapters relate to various aspects of osteoporosis, though in a few cases the relation seems remote. The final chapter by Donald Whedon critically reviews the entire area covered by the essayists. Several chapters bring new information to bear, while others arouse a sensation of déjà vu.

One of the editor's principal difficulties is that the term "osteoporosis" conveys different connotations to his individual contributors. He has solved this problem by allowing each author to use the word in his own way. Lack of specific definition leads to considerable confusion; in some chapters, osteoporosis is treated as a single condition, while in others the clinical, chemical, radiological, and kinetic heterogeneity of the various osteoporoses is emphasized. One author even tries to make a case for a parathyroid etiology for postmenopausal osteoporosis, based on radiolucency of bones in hyperparathyroidism and density in hypoparathyroidism. Unfortunately, no direct or indirect measurements of parathyroid function in osteoporosis are presented.

From the standpoint of the clinician, several chapters are of particular value. Marshall Urist of UCLA writes from the vantage point of long observation and imaginative study of many patients with "pathologic" postmenopausal osteoporosis. He and his co-workers have carefully matched their living patients with comparable autopsy specimens and point out the association of vertebral deformity with pathological osteonecrosis. They differentiate between the normal loss of bone substance with age and that associated with symptomatic, deforming, pathologic osteoporosis. They, and most of the other writers, emphasize the relative rarity of osteoporosis in men. They also lay the myth of calcium deficiency in patients with severe disease, and point out that a third of their patients with pathologic osteoporosis give a history of a diet rich in dairy foods.

Siegelman's chapter on the radiology of osteoporosis is



one of the most lucid and accurate descriptions available. Since the various osteoporoses have different radiologic appearances, Siegelman well illustrates three of the most important types: that of immobilization, that produced by excess glucocorticoids (with its pathognomonic eburnation of the vertebral endplates), and that of osteogenesis imperfecta. While the most common postmenopausal type is not illustrated, it is clearly described.

Rose makes a most valuable clinical point, well known to students of bone diseases, but poorly popularized and essential for evaluation of therapy. He points out that in adults loss of bone is irreversible. Thus, it is too much to expect to see restoration of bone substance, even by the most sensitive techniques. Since bone restoration is not accomplished by any form of treatment, methods for demonstrating that a proposed treatment can stop bone loss are an important part of any discussion of osteoporosis. Neither the Meemas nor Cameron have a chapter on their elegant, objective methods of measuring bone density, though Erik Meema participated in discussion.

The Cameron technique is described by Davis et al., from the University of Chicago, who review their published evidence that estrogens retard bone loss after the menopause. Bauer's review of the epidemiology of fractures, previously published elsewhere, also emphasizes the sex-linked nature of bone fragility, as evidenced by the increased incidence of fractures in postmenopausal Swedish women. Ethnic susceptibility is also described. Several authors comment on the relative lack of osteoporosis in Negro populations. Makin et al. confirm the more frequent occurrence of hip fractures in women over the age of 50 and show that in Israel this excess is limited to women of European or American origin, while the Afro-Asian group shows no significant increase.

Unfortunately, the chapter on the role of fluorides was not included in the final publication. It would be of interest in view of suggestions that induced fluorosis may be effective in treating some types of osteoporosis. The discussion, however, emphasizes the seriousness of endemic fluorosis, the fact that the bone is abnormally brittle, that neurologic complications are frequent, and that a fall on a rigid spine of breakable bone can be fatal in a person with endemic fluorosis.

It is of interest that the proponents of calcium therapy have changed the rationale of this investigational treatment from deposition of calcium in bone to inhibition of bone resorption, possibly by stimulation of endogenous calcitonin. Looking at James Arnold's beautiful vertebral preparations in this volume, it is obvious that osteoporosis is characterized by a dearth of bone tissue to be calcified. The concept of calcium deposition has long been untenable since, as Ernest Schwartz points out, it is not accompanied by phosphate retention.

It is apparent from this volume that each expert rides his own hobby, that osteoporosis is a heterogeneous group of conditions, and that no single treatment for these various conditions can be expected to provide a panacea. It is also clear that several currently investigational therapies can be expected to carry their own toxicity. The clinician will have to decide in each case whether the hazard is worth the possible benefit.

The volume has been beautifully printed on glossy paper with excellent reproduction of x-ray films and charts. As the editor points out, it is not intended as a textbook. The clinician will find the well-written chapters by Urist et al., by Siegelman, by Davis et al., and by Rose, well worth reading.

GILBERT S. GORDAN, M.D., PH.D.

**GENERAL PATHOLOGY—Fourth Edition**—Edited by Lord Florey, Provost of The Queen's College, University of Oxford, W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 1259 pages, with 575 illustrations on 484 figures, 7 color plates, \$24.00.

This book, as in earlier editions, has a distinctive character through its focus upon the interpretation and understanding of tissue changes in disease. With this approach to "General Pathology" it has no sections on diseases of organs, and relatively few specific diseases are segregated, although atherosclerosis and tuberculosis have special chapters. Tumors and viral diseases are considered as groups of related conditions. This type of presentation is not encyclopedic, but, together with the readable style, it provides interesting reading, and reference to a specific subject brings the reader in touch with a variety of well-presented related material. Using the book is like making a trip. The primary purpose is expanded by the many points of interest along the way.

The book is presented by its 20 co-authors as a memorial to Lord Florey who died as it was nearing completion. This edition retains the form of its predecessors but has been rewritten in some sections. Two chapters have been eliminated and one on "Pathological Consequences of Chromosomal Abnormalities" has been added. With these successful moves toward updating the book, it is unfortunate that the ambiguous term, hyaline degeneration, has been perpetuated. This includes such unrelated processes as aging of scars, deposits of resorbed protein in renal tubular cells and changes associated with injury to liver cells.

The subject of the book is general pathology in the broadest sense. The volume should be of value to anyone who has a fundamental interest in disease.

ALVIN J. COX, M.D.

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**SURGERY—Principles and Practice—Fourth Edition**—Jonathan E. Rhoads, M.D., D.Sc. (Med.), John Rhea Barton, Professor of Surgery, School of Medicine, University of Pennsylvania, Philadelphia; J. Garrott Allen, M.D., Professor of Surgery, Stanford University Medical School; Attending Surgeon, Stanford University Medical Center, Stanford; Henry N. Harkins, M.D., Ph.D., Late Professor of Surgery, University of Washington School of Medicine, Seattle; and Carl A. Moyer, M.D., Formerly Bixby Professor of Surgery, Washington University School of Medicine, St. Louis. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. (19105), 1970. 1864 pages, 758 illustrations, \$24.00.

With publication of the fourth edition, *Surgery—Principles and Practice* becomes even more firmly established as one of the basic surgical texts for the student and House Officer. The fourth edition is also the end of a cycle in which each one of the four original editors has now had the opportunity to leave his particular mark as the senior editor. The excellent chapters on Nutrition, Parenteral Alimentation and Fluid, and Electrolyte Balance reflect the ongoing interest and continuing contributions of this edition's senior editor, Dr. Rhoads.

There are several factors distinguishing this edition from its predecessors:

A notable loss is the History of Surgery chapter, parts of which have been incorporated under the individual sub-topics which make up the book's chapters. Although the surge for new knowledge and new areas of surgical application has blunted the interest in surgical tradition and history, it seems that this is the place where the student should be oriented to the continuity of surgical experience and the evolution of surgical techniques and research. New disciplines, as reflected in the new chapter Tissue and Organ Transplantation, do not arrive *de novo* but are inexorably linked with each step that went before it. Introducing the student to the history and methodology of surgical innovation is still study of the History of Surgery.



Another new chapter, *The Molecular Attack on Cancer* is a valuable addition to this new volume as an introduction to the subject. It would seem that this chapter could be expanded, particularly to reflect the waning interest in cancer chemotherapy and the exciting new developments in tumor immunology.

The chapter on *Military Surgery* has been expanded to include the experience of the Vietnam War and is augmented by photographs and descriptions of newer concepts in resuscitation, evacuation and early care of the traumatized patient.

The final chapter on *Mathematical Analysis of Surgical Data* should provide the student with some basic tools for assessing the significance and experimental discipline of many of the concepts he will be reading when he moves beyond the textbook stage.

The original design of the book, to provide a uniform approach yet reflect the basic thinking of the foremost surgical teachers in different areas, has been well preserved.

HERBERT I. MACHLEDER, M.D.

**MEDICINE AND STAMPS**—Edited by R. A. Kyle, M.D., and M. A. Shampo, Ph.D. Published by the American Medical Association, 535 North Dearborn Street, Chicago (60610), 1970. 216 pages, \$1.00.

"Medicine and Stamps," edited by R. A. Kyle, M.D. and M. A. Shampo, M.D., published by the A.M.A. in 1970 records on 206 pages in alphabetical order the biographies of 160 different physicians and scientists.

This work is printed on glossy paper and is of excellent legibility. With very few exceptions a full page has been allocated to each item. Next to the title a stamp, portraying the specific physician, is shown in black and white and enlarged as prescribed by law. Scott Catalogue numbers, country and year of issue, and identification of the particular author appear at the end of each biography. Between pages 110 and 111 there is a double page of special glossy paper, like the very attractive book jacket, entitled: "Representative Stamps Honoring Medical Pathfinders and Illustrious Practitioners." While the stamps shown on the double page are considerably reduced in size, those on the jacket are even more enlarged than those embellishing the biographies. The stamps on the jacket and on the double page are shown pretty close to their original colors.

Besides an informative foreword and the Table of Contents (7 pages)—listed alphabetically by the countries that issued the stamps shown—there also is an index of seven pages. Here the various personalities are listed under headings indicating their special field(s) of activity—a very useful addition.

As to the biographies, they are mostly of a basic quality, especially so if compared with those in the well known ATA Handbook No. 39 "Medical History in Philately" by Dr. G. Newerla, a highly esteemed member of the American Topical Association (ATA)-Medical Subjects Unit and considered an authority in this field, and in "Doctors Philatelic" by Oscar Gottfried, also a greatly respected, scholarly member of the ATA Medical Subjects Unit. His soft-cover book, containing 283 biographies, each with a portrait stamp, and also a very useful bibliography, has four supplements, bringing the whole collection up to October 1966. (Incidentally, no more supplements can be expected because—most regrettably—the author had to discontinue them for reasons of ill-health).

It would have been an appreciable improvement of the book's value, had such a cut-off date been added. But even if July 1961, as mentioned in the Foreword, would have to be considered as a limit, it would seem that many

important personalities have been omitted within the scope of the presentation. For this exclusion various reasons could fairly be stated but as none has been specified the reviewer is unable to express an opinion in that regard.

R. L. BALLIN

**THE NEW SOCIAL DRUG—Cultural, Medical, and Legal Perspectives on Marijuana**—Edited by David E. Smith, M.D., Medical Director, Haight-Ashbury Medical Clinic; Consultant on Drug Abuse, San Francisco General Hospital; Assistant Clinical Professor of Toxicology, University of California, San Francisco Medical Center, Prentice-Hall, Inc., Englewood Cliffs, New Jersey (07632), 1970. 186 pages, \$5.95.

This is a collection of eleven articles addressed to presenting informed material about marijuana. One is an original article, one is reprinted from *Science*, one is reprinted from the *Journal of Health and Social Behavior* and eight are reprinted from the *Journal of Psychedelic drugs*, edited by the editor of this volume. In general, all the articles are well written and constitute major and substantive contributions. The gathering of these together under one cover is an obvious attempt to promote one point of view as intimated by both the title and the Introduction. This is the soft-sell for use whereas in the past there has been a hard sell for abstinence. In this reviewer's opinion neither point of view is appropriate for reasoned scientific presentation or for responsible popular reporting. The assumption is that now that our society has finally found the pharmacological cookie jar—as pressures of super-industrialization mount—our tie to reality and subsequent defense will be our hand in the jar. Each will work out his own Social Drug and the case presented in this volume is that marijuana should not be excluded as an option. The editor and author may protest "misinterpretation," but the choice of title and content of the Introduction leave no doubt as to the point of view. The reviewer recommends the book for the value of the individual articles and for the convenience that they are bound together.

KEITH F. KILLAM, PH.D.

**MORE THAN SKIN DEEP**—Thomas H. Sternberg, M.D., Professor and Chairman, Division of Dermatology, School of Medicine, University of California, Los Angeles. Doubleday & Company, Inc., 277 Park Avenue, New York, N.Y. (10017), 1970. 330 pages, \$7.95.

According to the author this book was written to satisfy the vast reservoir of interest and concern about one's skin among those millions of people who never find occasion to visit a dermatologist. It is an attempt to explain in layman's terms the signs and wonders of the human skin. It is concerned with beauty and the appearance of the skin as well as its medical aspects and the aging process. It also is meant to teach its readers the skin changes which indicate the need to see a physician.

In the foreword there is a discussion of the anatomy and physiology of the skin. It details some of the physical and chemical agents and microorganisms to which one's skin is constantly exposed and mention is made of the skin's many and varied attributes which allow man to adjust to his environment.

Part One of the book is titled "A Dermatologist Talks About Beauty." This occupies 138 pages and includes chapters on general skin care, cosmetics, nails, hair, pigmentation, aging skin, reactions to medications and body odor.

Part Two is 68 pages long and is entitled: "A Dermatologist Talks About a Program of Skin Health Throughout Life." Chapters are devoted to pregnancy and the skin,



the pill, the skin and its care during infancy and early childhood, bugs, bites, and itching, puberty, adolescence and acne, hazards to the skin at work and at home, and maintaining good skin health in old age.

Part Three includes 103 pages under the heading: "A Dermatologist Described the Major Diseases of the Skin for the Layman." Chapters include systemic diseases of the skin, systemic infections with skin manifestations, benign tumors, skin cancers, collagen diseases, psoriasis, the skin in relation to cardiovascular disease, the endocrine glands, diseases of the lips and mouth, treatment, the nervous system and the skin, psychoneurosis and the skin. There is a good index.

At the end of each chapter in the first two parts of the book and at the end of the third part there are questions and answers based on the material presented. This involves some repetition. There is also some duplication of material in the three major sections of the book. The author recognizes and justifies this for handy reference.

I asked several non-medical people to read the chapter headings and some of the material. All expressed keen interest and asked to have the book for more complete examination. Nurses, secretaries, and other paramedical personnel will find this an excellent reference regarding skin diseases.

Dermatologists will find some subjects where they differ in point of view and emphasis with the author but very little on which there will be frank disagreement.

All physicians concerned with skin problems would do well to be aware of the book. Patients who have read it are sure to compare opinions and advice given them by their doctor with those expressed by the author.

H. V. ALLINGTON, M.D.

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**OTORHINOLARYNGOLOGIC RADIOLOGY—A Radiologic Atlas of Ear, Nose and Throat Diseases**—Richard Mittermaier, University Ear, Nose and Throat Clinic, Frankfurt am Main; English edition arranged by Paul W. Hoffmann, Department of Otolaryngology and Maxillofacial Surgery, University of Cincinnati. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 403 pages, 694 illustrations, \$38.50.

This book does a good job of reviewing clinical radiology in the ear, nose and throat area. Its strong point is the clinical summary provided with each of the X-rays. My only criticism is that it does not contain a section on laryngograms as developed by Powers, et al., at Washington University in St. Louis.

In summary, I feel that it fills the need for a clinically oriented ear, nose and throat radiology atlas.

HERBERT H. DEDO, M.D.

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**TRIGEMINAL NEURALGIA—Pathogenesis and Pathophysiology**—Edited by Rolf Hassler, Professor, Max-Planck Institute for Brain Research, and A. Earl Walker, M.D., Johns Hopkins University School of Medicine, with 28 contributors. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 196 pages, 155 illustrations, \$15.50.

This detailed volume on trigeminal neuralgia is extremely well edited, being very concise. It contains the work of twenty-eight contributors in some 196 pages. It offers a tremendous wealth of information to those investigating or treating pain syndromes. It fills a growing void, since the volume on *Trigeminal Neuralgia* by Stookey and Ransohoff was published in 1959. The authorities contributing to this present volume are world renowned for their specific contributions to this problem. The chapters on the underlying anatomy and physiology are extremely well done and contain much detailed information. The

compilation of this much basic material on one clinical syndrome in a single volume is, indeed, an impressive undertaking and should remain a real contribution for many years to come.

The volume, however, does have a few minor drawbacks. The unfortunate delay of almost three years from the meeting in Germany in October, 1967, until the present date of publication causes some of the material to be far from new. For those interested in researching deeply into the subject of trigeminal neuralgia, there is very little information in this volume that is not already available in the various specialty publications. Further, in the rapidly advancing field of medicine, there are further contributions on this subject of trigeminal neuralgia that have not been included. Lastly, the clinical aspects with discussions of decompression versus compression procedures and the results of some of the surgical operations are certainly somewhat confusing. Perhaps the weakest section is the final three chapters on causation of trigeminal neuralgia. This is, of course, understandable, since no one has as yet the final answer concerning etiology. However, those who stress peripheral etiology seem on balance to have been given disproportionate space to those who stress the underlying neurophysiological central mechanisms. Gardner's beautifully written and detailed chapter #21 on the causation of trigeminal neuralgia again apparently fails to comprehend the difference between a central lesion and a central mechanism initiated by a peripheral etiological lesion. However, his treatment of a peripheral short circuit reverberating reflex arc, as opposed to the alternative theory of central neuron repetitive discharge, is extremely well summarized.

BENJAMIN L. CRUE, JR., M.D.

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**DUNCAN'S DISEASES OF METABOLISM—6th Edition**—in Two Volumes—Vol. I: Genetics and Metabolism—Vol. II: Endocrinology and Nutrition—Edited by Philip K. Bondy, M.D., Professor of Medicine, Yale University School of Medicine; in Association with Leon E. Rosenberg, M.D., Associate Professor of Medicine and Pediatrics, Yale University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 1413 pages, \$39.00 (both volumes), \$21.00 (one volume).

Overall this edition is comprehensive, strong on fundamental mechanisms both in health and disease. The list of contributors is impressive and the scope is both broad and deep, especially from the viewpoint of the internist. The pediatrician will need another endocrinology text, especially for descriptions of ill-understood "endocrine" disorders.

The organizational plan is to present four parts: genetics, intermediary metabolism, endocrinology and nutrition, and it is a success. Some things I wanted to know had to be probed for in multiple places. I found the introductory chapters on genetics and intermediary metabolism excellent.

Because of my own bent I thought it would be worthwhile to keep a list of questions that I tried to look up and to write how I fared; some of these follow. Question—Should DBI be used to modulate brittle diabetes? The answer was available, and if one consulted the "recent developments" section, highly current. Question—What is the shape of the curve of concentration of immunoreactive insulin in plasma after glucose loading? The answer was available in terms of fasting and peak values in the section on diabetes; with further looking I found curves for the obese and normal subjects in the section on nutrition.

Question—How effective is each of the treatments of acromegaly in respect to the natural history of the disease, particularly the age at which death occurs and the



amelioration of symptoms? The answers were general. I could not find Beckwith's syndrome when I had need to advise on its course. I could not find the Prader-Willi syndrome, a disorder I needed to learn more about. I then tried the Lesch-Nyhan syndrome. It was one of 64 syndromes listed from those of Albright and Asherman to Zieve and Zollinger-Ellison. The direct listing was under phosphoribosyl transferase and the section, including purine metabolism, was excellent. In general, and probably altogether rightly, when the mechanism of the disease is known the book is comprehensive on the subject.

I found no description of juvenile hypothyroidism presenting as a problem in severe short stature but with normal mentation, and I am dumbfounded by the statement, "many cretins with treatment may demonstrate normal and even increased intelligence." Later the intractable child incapable of learning is cited but I think the emphasis is awry.

I recently strongly supported a medical review board that refused to pay for aqueous adrenal cortical extract for treatment of "hypoglycemia" only to find myself undercut by the recommendations in this book that it be used for thyroid storm. The editor, Professor of Medicine at Yale, made no mention of this extract in his own section on the adrenal cortex, and I think the fact he let this go into the thyroid section gives eloquent testimony to how harried the Yale faculty was by the student riots.

This book is a bargain at its price of \$38.00, well printed and illustrated, sometimes with color. It will best serve those who want to understand disease. From time to time it will be disappointing to those who want to know the details of management and its outcome.

W. P. VANDERLAAN, M.D.

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**HERMS'S MEDICAL ENTOMOLOGY**—Sixth Edition—Maurice T. James, Ph.D., Professor of Entomology, Washington State University, Pullman; and Robert F. Harwood, Ph.D., Professor of Entomology and Chairman, Department of Entomology, Washington State University, Pullman. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1969. 484 pages, \$15.00.

This edition of an outstanding text in medical entomology comes with improved format and organization, much new material, and the inevitably higher price tag. Since the first edition in 1915, entitled *Medical and Veterinary Entomology*, the book has remained an outstanding English-language text. The present, sixth, edition has Herms's name added to the title and is a worthy effort by two Washington State University entomologists, M. T. James and R. F. Harwood, to encompass the flood of new information and to recognize growing public concern over methods used to control arthropod vectors. The improvement in the book's appearance results from larger page size and an uncrowded 2-column format, and better paper quality that permits excellent photo reproduction and smaller but still highly legible type.

The book has a better organized and fuller consideration of disease agents. Many of the newly discovered arboviruses are now included, grouped according to the arrangement of Casals. Chemotherapy for malaria and filariasis is added. Specific control methods for mosquitoes, flies, and other groups are now combined in a single chapter, with consideration of the principles of arthropod vector control. This permits the student to focus on the ecological problems tied to insect control and on possible alternatives to the use of lethal broad-spectrum chemical agents.

A new chapter adds long-needed information on epidemiological methods, and on environmental factors,

which so strongly influence transmission of disease. But the consideration of zoonoses and the relationships between animal infection and outbreaks of human arthropod-borne disease still is weak. Some of the more detailed taxonomic material and tabulations of comparative morphology have been deleted but essential descriptive material has been retained. Greater knowledge of arthropod bloodsucking adaptations permits descriptions of sucking mouthparts of the various arthropods to be supplemented by a discussion of feeding mechanisms, reflecting Lavoipierre's elegant studies that distinguish between pool and capillary feeding.

A worthwhile addition, not so much for the factual value as for its probable stimulus to students to develop a broader biological outlook, is the discussion on the evolution of parasitism and of pathogen transfer. This chapter summarizes the authors' views on the probable evolution of blood and tissue feeding habits among arthropods. It suggests a possible sequence of ancient changes leading to blood and tissue feeding, then to the adaptation of infective agents within their arthropod hosts, and ultimately to the arthropod role as vectors of human disease.

This text applies to medicine largely at the levels of the student, the epidemiologist, and the public health specialist. I would also strongly recommend it, however, to physicians with an ecological viewpoint and to people concerned with problems of public health in developing areas.

DONALD HEYNEMAN, PH.D.

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**TEXTBOOK OF NUCLEAR MEDICINE TECHNOLOGY**—Paul J. Early, B.S., Physicist, Nuclear Medicine Institute, Cleveland, Ohio; Muhammad Abdel Razzak, M.B.B.Ch., D.M., M.D., Assistant Professor, Medical Unit and Division of Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, U.A.R.; and D. Bruce Sodde, M.D., F.A.C.P., Associate Professor of Radiology (Nuclear Medicine), George Washington University, Washington, D.C.; Director, Nuclear Medicine Institute, Cleveland, Ohio. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 378 pages, with 241 illustrations, \$15.50.

In this new and quite substantial textbook, the authors have attempted to fill a very definite gap in current texts on Nuclear Medicine. Because of its relative youth, the field of Nuclear Medicine is still seeking to establish its own set of fundamental yet comprehensive textbooks. The technologists in particular have lacked the appropriate book, which should be basic in its educational approach yet complete in its outline of the technical aspects of all radioisotope procedures. The present text attempts to fill this gap, a gap which has resulted from the complete absence of technological training programs in Nuclear Medicine until just recently, having arisen primarily from obvious need in one of the existing training programs, but it too has fallen short of the optimum in its presentation of clinical radioisotope procedures.

The book is divided into two sections. The first half is an extensive review of basic concepts in physics, radiation detection (both in principles and in specific counting and imaging devices), mathematics and statistics of various radioisotopic techniques, and some basic principles of radiobiology and radiation protection. This is by far the more effective half of the textbook, developing from the very basics all principles in the areas described which would be important to a technologist for a complete understanding of the tools with which he works. Practically no significant area of background in physics nor instrumentation is overlooked, yet each area is developed only to a stage of practical utility without a plethora of complex mathematical equations and physical concepts. It is the best basic background currently available to a tech-



nologist in training for an effective grounding in Nuclear Medicine.

A few additions to this half of the book would be helpful. Very little is said about the steadily expanding and rather complex realm of radiopharmacy, even though the Nuclear Medicine technologist today must have an increasing degree of sophistication in his knowledge of specific radiopharmaceuticals, their principles of action and utilization, etc. Related to this, an expanded discussion of generators would be helpful, including the equilibration curve following generator elution which plays a major role in decisions on repeated elutions of a given generator. In all likelihood we will see a progressively increasing use of generators in the average Nuclear Medicine Laboratory. Also helpful for general background in the area of radiobiology and radiation protection would be a greater emphasis on the role of beta particles in the radiation risk from a given isotope, rather than gamma emissions, and a chart of commonly used radioisotopes and radiopharmaceuticals documenting the radiation delivered to whole body and critical organ by a standard adult dose. Particular omissions in the area of radiation detection instruments include the absence of mention of positron imaging with the scintillation camera, a modality of imaging which should become increasingly important in the future both for its tomographic capabilities and for the fact that external collimation is eliminated; and the total absence of any mention of whole body counters as useful and relatively widely available instruments for certain routine and investigative radioisotopic procedures. Nevertheless, this first half of the text entitled "Nuclear Science" is one of the best basic backgrounds currently available to the training technologist, as well as resident or fellow in Nuclear Medicine.

Unfortunately, the second half of the text entitled "Clinical Nuclear Medicine" falls considerably short of what would be ideal or even optimal in such a book. Individual chapters on specific organs or systems elaborate initially on anatomy and physiology which is helpful to the person with a minimal biologic background, then progress to rather abbreviated descriptions of radioisotopic procedures in current use. Almost every important organ or metabolic study currently available is touched upon to some degree, and in this regard provides a relatively comprehensive background for a training technologist. However, descriptions of procedures are often too abbreviated, with minimal discussion of specific technical details which might otherwise make the book important as a reference source for procedure technique.

In red blood cell survival studies, for example, no comment is made upon spleen-liver ratio counting and the significance of the numbers obtained. No technical comments are made upon the problems of external organ localization and repeated counting in a ferrokinetic study, nor upon the importance of adequate probe shielding in such a study where a lightly shielded probe could introduce considerable extraneous counting activity. Simplifying the ferrokinetic red cell incorporation study by using the fifteen minute post-injection blood sample as the 100 percent starting level introduces an error of ten percent or more with a plasma disappearance half time of ninety minutes. No mention is made in spleen imaging of what has now become the commonest spleen label,  $^{99m}\text{Tc}$  sulphur colloid, one which need be replaced by other radiopharmaceuticals only when the spleen is obscured by extensive hepatic enlargement. No mention is made of the use of  $^{18}\text{F}$  as a bone scanning agent, a tracer which will find increasing use in the future, and brief mention of  $^{133}\text{Xe}$  as an inhalation and perfusion lung

tracer gives little information which would be helpful to a technologist beginning to undertake such studies, now becoming increasingly widespread. Although the authors describe choroid plexus labeling as a problem in brain imaging with  $^{99m}\text{Tc}$  pertechnetate, no mention is made of the use of iodides nor perchlorate as effective methods of blocking this labeling.

The chapter on renal imaging discusses scintillation camera usage only briefly, a fault noted repeatedly throughout the clinical section of the book, even going so far as to include an illustration of a  $^{99m}\text{Tc}$  pertechnetate renal blood flow study which is improperly referred to in the text and not expanded upon. Many sections would benefit from additional examples in the form of illustrations, such as comparisons of normal and abnormal Hippuran renograms, illustrations of one or two positive bone scans, comment upon cardiac blood flow studies for the assessment of pericardial effusions and subphrenic abscesses, etc. Additional comment might also be made upon newer techniques which will gain wider usage such as bone marrow imaging with radiocolloids, joint imaging with  $^{99m}\text{Tc}$  pertechnetate, similar imaging of abscesses which can also be effected with  $^{131}\text{I}$ -RISA, double isotope procedures such as combined liver and lung imaging for subphrenic abscess, etc. Many good illustrations are included of normal and abnormal studies both by rectilinear scanner and less frequently scintillation camera in the major organs of interest, however. The clinical section does give a good general background for the person new to the field, if not very helpful in the expansion of technical details and discussion of varieties of abnormalities. The glossary at the end of the clinical section seems particularly irrelevant to the training technologist, and the list of radionuclides in common use noted in the appendices overlooks some important isotopes such as  $^{14}\text{Carbon}$ ,  $^{55}\text{Iron}$ ,  $^{22}\text{Sodium}$ ,  $^{85}\text{Krypton}$  (instead of  $^{79}\text{Krypton}$ ), etc.

The overall impression one gets from the book is of a very good nuclear science section, developing the physics and instrumentation background quite effectively for the training technologist, but a very average clinical section which would require quite extensive supplementation in specific organ areas. In this regard, a more extensive bibliography subdivided by organ or system would be helpful. Nevertheless, the book should be very useful to any technologist training program for its many assets in spite of the shortcomings described.

DAVID C. PRICE, M.D.

**CLINICAL AIDS IN CARDIAC DIAGNOSIS**—William Dressler, M.D., Consultant in Medicine, Maimonides Hospital Medical Center, Brooklyn; Consultant Cardiologist, Veterans Administration Hospital, Brooklyn. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1970. 246 pages, \$12.75.

William Dressler book on physical signs in cardiac disease represents a "cri du coeur" of an "old fashioned" physician. It will be echoed by many in the field who decry the devaluation of the history and physical examination in patients with heart disease. Angina pectoris is not diagnosed by an electrocardiograph and/or even a coronary angiograph. The book presents the author's personal experience, involving the history, physical signs, electrocardiographs, phonocardiographs and apexcardiographs often in specific patients. The amount of detail given makes the book too meaty for medical students. It is perhaps more suitable for trainees or fellows in cardiology. The illustrations are numerous and of high quality with excellent legends. A greater emphasis on radiology to the exclusion of much of the section on percussion might improve the balance of the book.

MALCOM B. MCILROY, M.D., F.R.C.P.



# Amebiasis, Today, in the United States

ELIZABETH BARRETT-CONNOR, M.D., *La Jolla*

● *A most important factor in the detection of amebiasis is to entertain the diagnosis first. Appropriate search for the parasite should precede other diagnostic or therapeutic efforts which may mask the correct diagnosis for weeks. An alert suspicious physician with competence at the microscope can save the patient from amebic neurosis secondary to over diagnosis as well as chronic ill health and possible death related to underdiagnosis.*

ALTHOUGH MAN FIRST SAW the organism *Entamoeba histolytica* in 1875 and recognized its relationship to disease some ten years later, D'Antoni could say as recently as 1949 that "the majority of physicians know little about amebiasis and what knowledge they have is usually incorrect."<sup>1</sup> In view of increasing civilian and military travel as well as continuing endemicity of amebiasis in North America, it seems worthwhile to reemphasize this important infection as seen in the United States.

The diagnosis of amebiasis is subject to three major problems. One of them is clinical underdiagnosis. Amebiasis is often not considered unless the patient has recently returned from the tropics, but the interval between travel exposure and the development of overt disease may be over 30 years. While it is true that travel to developing countries enhances the likelihood of symptomatic disease, it is not necessary to have an exotic travel history to have amebiasis; by conservative estimate 5 percent of the untraveled U.S. population harbors *E. histolytica*.<sup>2</sup> A second problem, related to the poor correlation between the prevalence of amebas and amebic disease, results in

over-diagnosis of clinical amebiasis in response to a laboratory report of *E. histolytica*. It is well to bear in mind that at least 90 percent of persons who have *E. histolytica* in stools are asymptomatic cyst carriers whose present illness (if any) is totally unrelated to this finding. Unfortunately, as Elsdon-Dew has noted, amebas have been blamed for nearly every condition except pregnancy.<sup>3</sup> The third problem is missed laboratory diagnosis. Although laboratory proficiency is generally at a low level, many physicians rely entirely on the findings of their clinical laboratories to confirm or deny a diagnosis of amebiasis.<sup>2</sup> The difficulty in identifying *E. histolytica*, particularly from a symptomatic patient, has been over-emphasized, and every physician should attempt to identify this parasite himself. Prompt examination of a fresh stool specimen by a novice is frequently as informative as examination of an old stool, as received in the laboratory (where, by the way, it is often seen by an equally unexperienced technician).

## Etiology

Man becomes infected by ingestion of food or water contaminated with fecal material containing cysts of *E. histolytica*. Swallowed viable cysts liberate trophozoites in the intestine near the

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cecum. The motile vegetative trophozoite is the only form of *E. histolytica* which is parasitic in man. It is the bowel transit time which determines whether cysts or trophozoites are found in the stool: During normal slow passage through the colon, trophozoites encyst; with purgatives or diarrhea some trophozoites, carried rapidly to the outside, can be found in liquid stool.

It is unknown why the majority of infections, particularly those acquired in the United States, are asymptomatic. A good diet is believed to enhance commensalism and reduce pathogenicity of amebic infection. Travel, fatigue, stress, surgical operation or pregnancy precipitate symptoms in some patients. *E. hartmani*, formerly called small race *E. histolytica* (cysts less than  $10\mu$  in size), apparently never invades tissue and may account for many asymptomatic infections.<sup>4,5</sup>

### Clinical Diagnosis of Intestinal Amebiasis

Patients with amebiasis may present with acute febrile dysentery suggestive of shigellosis, with chronic dysentery or diarrhea suggestive of ulcerative colitis or regional enteritis, or with intermittent diarrhea or constipation suggestive of carcinoma of the colon. The illness may be of three hours' or 30 years' duration. Cases of long standing are frequently misdiagnosed as irritable colon or psychoneurosis. A complete review of amebic symptomatology is given in Wilmont's book.<sup>6</sup> Since symptoms are usually too non-specific to suggest the diagnosis, when evaluating a patient with complaints referable to the lower gastrointestinal tract, amebiasis must be considered first, before barium studies, mineral oil preparations, tap water enemas, or antibiotics obscure the diagnosis.

While typically the patient with uncomplicated intestinal amebiasis has no fever, anemia or leukocytosis, these systemic manifestations are seen with fulminating intestinal amebiasis. Death may result from failure to appreciate that amebiasis can cause severe illness. Corticosteroid therapy exacerbates intestinal amebiasis and surgical treatment of unrecognized amebiasis also carries a serious risk to life.

### Laboratory Diagnosis

Microscopic examination of the stool is the only sure way to establish the diagnosis of intestinal amebiasis. While the absence of pus

TABLE 1.—*Diagnosis of Intestinal Amebiasis*

Method	Diagnostic efficacy (Percent)
Microscopic examination of stool: without diarrhea—3 formed and 1 purged stool* . . . . .	90
with diarrhea—6 stools . . . . .	> 95
Sigmoidoscopy—pustules, ulcers or nodules	< 50
Barium enema—some abnormality . . . . .	25
Serologic diagnosis—IHA or agar gel . . . .	85

\*Two ounces of saturated solution of sodium sulfate is the best purgative and will result in a diarrheal stool within 4 hours (usually less). The diagnostic efficacy of stool examination assumes that the patient has not received barium or mineral oil preparations within the preceding 2 weeks; and has not received antibiotics within the past month; these procedures will often eradicate identifiable amebas without curing the patient.

cells or the presence of Charcot-Leyden crystals is suggestive, the identification of the parasite is necessary to confirm the diagnosis. In more than 90 percent of patients with symptoms due to intestinal amebiasis the organism will be found in fecal specimens if they are examined correctly—repeatedly if necessary—before other diagnostic or therapeutic measures are taken.<sup>7,8</sup> (Table 1). Specimens obtained by proctoscopic examination or in the course of rectal biopsy are rarely diagnostic in the face of negative stool examinations, except for patients in whom diagnostic efforts or antibiotics have obscured the presence of the ameba. If material is to be obtained at direct examination, solid objects such as spatulas or pipettes should be used rather than cotton swabs, for ameba may cling to swabs and not be transferred to the slide. Patients with diarrhea need no preparation for sigmoidoscopy; for those who do not have diarrhea preparation should be done with a normal saline solution enema (not tap water or soapsuds).

All stool specimens should be examined fresh. Warming will not restore motility, and may dry out and destroy trophozoites. A pin-head size piece of stool is sufficient. The preparation should be thin enough to read newsprint through. With most specimens this requires dilution with saline solution, which should be placed on the slide before the stool is added. (Water should not be used, as it will alter trophozoites.) Examination of unstained specimens should start under low power, with higher magnification used for delineation of suspicious findings.

The distinguishing features of *E. histolytica*

TABLE 2.—*Identification of E. histolytica (large race)*

	<i>Unstained</i>	<i>KI (D'Antoni's)</i>	<i>Iron-hematoxylin</i>
Trophozoite	Progressive motility  Clear pseudopod  Invisible nucleus  Ingested RBC		Delicate nucleus with central karyosome
Cyst	Small pearls, identifiable as <i>E. histolytica</i> only when chromatoid bars with rounded ends (sausages) are seen	1-4 ring-like nuclei 2 times RBC size	Delicate nuclei with central karyosome Rounded chromatoidals

Note: Unstained smears are best for identification of trophozoites; iron hematoxylin may be required for identification of cysts or of trophozoites which have lost their motility. Not all findings are necessarily present; *i.e.* *E. histolytica* trophozoites may have no ingested erythrocytes; cysts, no visible chromatoidals.

In contrast, the trophozoites of *Entameba coli* have sluggish non-progressive motility, granular cytoplasmic pseudopods, and a usually visible nucleus in the unstained preparation. Cysts of *E. coli* are approximately twice the size of *E. histolytica*. They contain up to 8 nuclei which are visible in unstained preparations and show a coarse nuclear pattern with a larger excentric karyosome in stained preparations. Chromatoidals, when present, have ragged ends.

are noted in Table 2. While "rip-snorting, galloping, blood-thirsty" trophozoites<sup>3</sup> are characteristic of amebic dysentery, in patients who do not have dysentery the parasites are often somewhat less active and contain debris rather than erythrocytes. Such forms may require stained preparations for differentiation from *Entameba coli*, other amebas, macrophages and the like. To avoid overdiagnosis: When in doubt, throw it out—*E. histolytica* looks remarkably like *E. histolytica*!

Unpurged specimens in chronic or asymptomatic cases may contain only cysts. In unstained preparations cysts resemble small pearls which cannot be separated from those of *E. coli* unless chromatoid bars with rounded ends are visible. Cysts are better identified in fresh specimens by staining with D'Antoni's solution, which demonstrates the number of nuclei, or by iron-hematoxylin staining which demonstrates nuclear structure. Chromatoidals are also visible with the latter stain, and it also permits preservation of slides for mailing when diagnostic confirmation is necessary. Stool can also be preserved in polyvinyl alcohol (PVA) fixative for examination at a later date.

The number of cysts in the stool varies from day to day; intervals of several weeks may pass between positive stools.<sup>9</sup> Concentration techniques, such as the zinc sulfate method, increase the diagnostic yield in such cases.<sup>10</sup>

As noted in Table 1, other diagnostic methods

are inferior to appropriate stool examination. Abnormalities on sigmoidoscopic examination are seen in less than half of cases, reflecting the greater frequency of cecal than rectosigmoid infection.<sup>11</sup> Occasionally sigmoidoscopic findings are sufficiently characteristic to suggest a diagnosis of amebiasis even without previous suspicion.<sup>12</sup> Ulcers, usually covered with a white cap, lying on normal intervening mucosa are suggestive. If the ulcers are elongated (like a knife-cut), or if scraping leaves a bleeding base much larger than the ulcer appeared superficially (collar-button ulcer), a presumptive diagnosis of amebiasis can be made. Confirmation by finding typical trophozoites is not difficult in such cases and should always be attempted.

Barium enema study is likewise a low-yielding diagnostic method for amebiasis, with abnormalities observed in less than 25 percent of cases.<sup>12</sup> Individual ulcers are usually too shallow to be seen roentgenographically, although multiple ulcerations may result in minimal irregularity or granularity of the mucosal pattern best seen on post-evacuation films. Granularity, lack of distensibility and narrowing of the lumen, which are the most common radiographic findings,<sup>13</sup> are not specific for amebiasis. A less common but more helpful finding is concentric inflammatory involvement of the cecum, often with a skip area of disease in another segment of the bowel, especially the rectosigmoid area; if skip lesions are present and the terminal ileum is normal,



ulcerative colitis or regional enteritis is unlikely. An ameboma usually appears as symmetrical concentric narrowing of the cecum without rigidity, features which make it readily distinguishable from the asymmetrical irregular defect seen with carcinoma of the cecum.

Serologic techniques are now available for the diagnosis of amebiasis. Indirect hemagglutination tests and agar gel diffusion give positive results when significant tissue invasion has occurred, but are usually negative for asymptomatic patients.<sup>14</sup> Thus a positive result is most likely to be obtained from the patient with typical trophozoites in the stool. Unless one of these methods is available locally, the loss of time involved in awaiting results is a serious objection to serologic methods for the primary diagnosis of intestinal amebiasis. They are, however, occasionally useful for retrospective confirmation when use of mineral oil, barium or antibiotics has obscured the value of stool examination.

## Diagnosis of Liver Abscess

Amebic liver abscess occurs in less than 1 percent of patients with intestinal infections, but recognition and treatment of it may be a medical emergency. Fever is the most frequent manifestation that brings the patient to the doctor.<sup>15</sup> A typical patient also has an enlarged tender liver, anemia and leukocytosis, but one or more of these findings are absent in up to 15 percent of cases.<sup>15,16</sup> Less than half of patients with amebic liver abscess have a recent or remote history suggestive of intestinal amebiasis.

Table 3 summarizes the diagnostic approaches to amebic liver abscess. Hepatomegaly is the most frequent sign, provided careful attention is paid to upward as well as downward enlargement and chest roentgenograms are used to supplement physical examination. Elevation of the diaphragm—classically, anterior medial bulging—or immobility of the diaphragm is observed in more than 80 percent of patients.<sup>16</sup> Blunting of the costophrenic or cardiophrenic angle or plate-like atelectasis of the right lower lobe are helpful features when present. A crescent shadow superimposed on the denser shadow of the hepatic cupola is also suggestive. Later, sympathetic or communicating pleural effusions or pneumonia may be seen. One or more abscesses, usually in the right lobe of the liver, can be lo-

TABLE 3.—Laboratory Diagnosis of Amebic Liver Abscess

	Percent of Cases
Liver function tests (alkaline phosphatase, BSP) elevated in . . . . .	< 25
Stools for <i>E. histolytica</i> positive in . . . . .	< 50
Chest x-ray—elevated diaphragm, blunted costophrenic angle, atelectasis, effusion or pneumonia . . . . .	80
Chest fluoroscopy—altered diaphragmatic motility . . . . .	85
Liver scan (AP and lateral)—filling defect . . . . .	95
Serologic tests (IHA or agar gel diffusion) . . .	95
Aspiration of abscess—sterile pus of any character . . . . .	85
Identification of amebas (serial tubes) . . . . .	90
Liver biopsy of abscess wall . . . . .	70

calized by radioactive liver scan in the majority of cases.<sup>17</sup>

While drainage is not necessary in the majority of patients with amebic liver abscess, some will not respond to anti-amebic therapy until drainage has been carried out. Aspiration through a large-bore needle (required for withdrawal of thick pus) is usually associated with a dramatic decrease in both pain and fever. The hazards of closed aspiration of amebic liver abscess have been over-emphasized in the American literature. Aspiration of a liver abscess, especially one localized by scan or by point-tenderness or bulging on physical examination, provides the most secure differentiation between amebic and pyogenic liver abscesses. The aspirate may have any appearance; but chocolate or gelatinous red pus or sterile pus (less than 15 percent of amebic liver abscesses are secondarily infected) is very suggestive of an amebic liver abscess. When aspirate is divided into serial specimens as it is withdrawn, examination of the last specimen, representing the edge of the abscess, will demonstrate trophozoites in 90 percent of cases.<sup>3</sup> Biopsy of the edge of the abscess has also been successful for diagnostic confirmation.<sup>18</sup> To obtain the specimen, a Vim-Silverman needle (outer core only) is introduced until pus is aspirated and then withdrawn just to the point when pus can no longer be obtained. At that point the split inner needle is introduced and the biopsy specimen is taken in the usual way.

If aspiration is not attempted, the patient can be treated for both pyogenic and amebic liver

TABLE 4.—Treatment of Amebiasis (adult dose based on 60 kg man)\*

Condition	Drug	Dose	Duration
A. Mild or asymptomatic intestinal infection.....	diiodohydroxyquin	650 mg tid	20d
B. Symptomatic intestinal infection without fever or leukocytosis.	tetracycline	250 mg tid	5d <i>plus</i> A,D <sup>°°</sup>
C. Severe intestinal disease (fever, leukocytosis, toxicity).....	emetine hydrochloride	1 g qd	5d <i>plus</i> A,B,D <sup>°°</sup> †
D. Liver abscess .....	emetine hydrochloride and chloroquine phosphate	1 g qd 1 g qd ff by 500 mg qd	10d <i>plus</i> A†† 2d 20d

\*The dosage varies by weight; emetine in particular must be given on a weight basis (1 mg per kg of body weight, not to exceed 65 mg). Emetine is given subcutaneously or intramuscularly; all other medications are given orally.

\*\*Patients with no evidence of liver disease should receive chloroquine.

†Tetracycline should be given concomitantly with parenteral emetine for severe amebic dysentery. Diiodohydroxyquin and chloroquine are best given after the course of primary therapy for intestinal amebiasis is completed.

††Patients with no evidence of intestinal infection should receive diiodohydroxyquin.

abscess while awaiting results of serologic study of specimens mailed to a regional laboratory or the Center for Disease Control in Atlanta. The indirect hemagglutination test and agar gel diffusion method are positive in more than 95 percent of cases.<sup>14</sup>

It is well to remember that the two diagnostic methods most often used, although helpful when positive, are more frequently normal. Results of liver function tests (alkaline phosphatase and bromsulphalein) are within normal limits in approximately 75 percent of cases, and stools are positive for amebas in less than half.<sup>15,16</sup>

### Treatment of Amebiasis

The chemotherapy of amebiasis has been unsatisfactory, as attested by the number of available drugs and the divergence of opinion in the literature about the drug of choice. The therapeutic quandary is compounded by the toxicity of the most active drugs, the usual need for at least two agents (a poorly absorbed drug effective in the tissue lumen against cysts and another drug for the trophozoite tissue phase) and the difficulty in differentiating relapse from reinfection in many endemic areas where drug trials have been conducted. No treatment is effective in all cases, and repeated stool examination for at least six months is necessary for confirmation of cure.

Controversy also clouds the merits of treating asymptomatic patients. Autopsy demonstration of bowel pathology in "healthy carriers" who died in accidents<sup>19</sup> and the sigmoidoscopic observation of abnormalities in up to 20 percent of asymptomatic cyst passers,<sup>20</sup> suggest that therapy should be carried out in all diagnosed cases

in this country. Other valid arguments for the treatment of asymptomatic amebiasis include the potential for the infections of others and the possibility that the disease may become severe—and not properly attributed—following one of the poorly understood events which upset host-parasite balance.

Table 4 lists a reasonable treatment regimen meeting Food and Drug Administration approval. Patients with intestinal infection and no evidence of hepatic amebiasis should receive a course of chloroquine to circumvent the development of an unrecognized amebic liver abscess at a later date. Patients with liver disease should receive treatment for intestinal infection also, whether or not amebas are found in the stool. Fulminating intestinal amebiasis (characterized by dysentery, fever and leukocytosis) and amebic liver abscess are potentially fatal conditions and merit the most rapidly active drug, emetine, despite its well-known cardiovascular toxicity. Unfortunately, patients have died or have suffered needless complications because emetine was withheld on grounds of toxicity.

Combinations of drugs are usually required because some—diiodohydroxyquin by mouth, for example—have direct action only on parasites in the bowel lumen; some, such as the tetracyclines, have indirect action on the bowel lumen and bowel wall but no effect on amebas in the liver; some, such as parenteral emetine, are effective only in the tissues (bowel wall and liver); and some are effective only in the liver, chloroquine for example.

Mctronidazole (Flagyl®) and niridazole (Ambilhar®) are the first drugs to be effective against



both intestinal and extraintestinal parasites. While the latter has been too toxic for general use, experience with Flagyl outside the United States suggests that it is safe, highly effective and currently the drug of choice for amebiasis.<sup>4,5,21</sup> The dose is 750 mg three times a day for five days for dysentery, 500 mg three times a day for five days for liver abscess. Unfortunately Flagyl has not yet received FDA approval for the treatment of amebiasis, and its use in most hospitals in the United States will therefore require approval of an experimental drug protocol.

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## EARLY CHANGES OF GLAUCOMA

"A great variation exists in the size and configuration of normal physiologic optic disc cupping. This variation makes difficult the detection of earliest glaucomatous disc changes. If the examiner searches for widening of the cup as an early change, he is at a serious disadvantage if he does not have a clear record of the base-line size of a specific optic disc cup. If the examiner searches for the development of a furrow in a margin of the cup or for extensive shelving of the disc rim or for obvious signs of atrophy, such cases are often already associated with significant visual field loss. Yet since tonometry may at times be misleading and since precise examination of the visual fields is not widely practiced on a routine basis, the detection of early glaucomatous disc changes is highly desirable. Although the cupping of the individual disc may vary widely, cupping is almost always symmetrically similar in the two eyes of an individual. . . . Any asymmetry of disc cupping is an important alerting sign of possible glaucomatous change.

"For the ophthalmologist, the importance of recognizing asymmetrical cupping is in its indication of the need for further evaluation. For the non-ophthalmologist who routinely uses the ophthalmoscope but not the tonometer, disc asymmetry represents the most accessible early sign of glaucoma."

—RONALD S. FISHMAN, M.D., Washington, D.C.  
Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 17, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# Complications of Rubella Immunization in Children

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■ *A rubella vaccine, prepared in dog kidney cell culture, was given to 4,734 primary school children in one California county in May, 1970. Adverse reactions of arthritis, arthralgia and paresthesia were reported two to eight weeks later. Paresthesia was a very prominent complaint and showed a peculiar diurnal pattern. Objective findings in a group of symptomatic children who came to medical attention were limited to tender, swollen, small joints. Rubella virus was isolated from throat swabs from two children with symptoms 38 and 43 days after immunization.*

*A sample telephone survey of immunized and non-immunized children was conducted two to three months after the vaccination program to estimate the frequency, type, and distribution of reactions. Approximately 7 percent of inoculated children had symptoms subsequent to vaccination. Almost no reactions were found in the control group. There was a preponderance of girls affected, but symptoms appeared to be more severe in boys. The highest complication rate was found in the youngest age group.*

*These reactions should be brought to the attention of medical groups and the public, but since these reactions are usually mild and self-limited, ongoing immunization programs need not be altered.*

ADVERSE REACTIONS TO RUBELLA immunization in adolescent and adult females are well recognized and have received considerable attention.<sup>1</sup> Observed reactions consist mainly of arthritis and arthralgia and occur with relatively high frequency in susceptible women. Recent information from large scale immunization programs conducted in many states indicates that similar reactions also occur in children.<sup>2</sup> This report

describes the nature and extent of reactions to a rubella vaccine given in a school immunization program in one California county.

## Materials and Methods

### *Immunization Program*

Toward the end of May, 1970, school children from kindergarten through the fourth grade in San Luis Obispo County were offered rubella vaccine in a program supported by several county organizations, the local medical society, offices of education and the local health depart-

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ment. Rubellogen,<sup>®</sup> a live attenuated virus vaccine prepared in dog kidney cell culture (Parke-Davis), was given throughout most of this program.

Of 8,376 children enrolled in kindergarten through the fourth grade, 4,734 (56.5 percent) were immunized during an 11-day period, May 18 to 28, 1970. With the exception of less than 30 doses given in one small school clinic in an outlying area of the county, all of the vaccine used was from a single lot of Rubellogen<sup>®</sup> (R915F2).

### *Clinical and Laboratory Study of Children with Vaccine Reactions*

Immediately following administration of the vaccine no early reactions (other than occasional soreness at the site of injection lasting for a day or two) were observed or reported. Approximately one month after the immunization program, the local health department received several reports of paresthesia and pain in extremities among children who had received the rubella vaccine. In response to these initial reports, the local health officer alerted the medical community and requested physicians to report all possible vaccine reactions. All of the patients referred by physicians were examined by one or another of two of the authors (H.K. or S.B.W.). In addition, throat swab specimens were obtained from nine patients for virus isolation attempts, and from eight of these children blood samples were also collected for rubella antibody determinations.

### *Telephone Sample Survey for Vaccine Reactions*

As it became apparent that late occurring paresthesia and other reactions being reported were associated with the vaccine, a sample survey by telephone was developed to estimate the frequency, type and distribution of reactions. This survey was conducted from July 20 through August 20 among two groups of school children—one group which had received vaccine in the school program and another which had not received vaccine. Parents were asked if their children had any complaints referable to arthralgia or paresthesia during the months of June and July. Many parents indicated that their children frequently had various aches and pains which

they considered normal childhood symptoms or "growing pains." Only the instances in which the parent could recall the exact or approximate date of onset, the duration and nature of symptoms, and could describe which extremity or extremities were involved, were recorded for the purpose of this survey.

## **Results**

### *Clinical Study*

Twenty-three children with probable reactions to rubella vaccine were initially reported by physicians to the local health department and examined by two of us (H.K. and S.B.W.). These children are listed in Table 1. They were equally distributed by sex; 11 of the 23 (48 percent) were male. Most of the children (14, or 61 percent) were 6 years of age or less.

The interval from immunization to onset of symptoms ranged from 21 to 54 days, with a mean of 34.6 days and median of 35 days. Duration of symptoms ranged from 4 to 26 days, with a mean of 16.6 days and a median of 18 days. Complaints were restricted to the upper extremities in 17 of the 23 (74 percent), to lower extremities in 2 of the 23 (9 percent), and involved both upper and lower in 4 (17 percent). In all 6 patients with lower extremity involvement (whether pure or mixed with upper limb involvement), both lower limbs were affected; in those with only upper extremity involvement, unilateral symptoms were common (10 of 17 patients, or 59 percent).

The first seven children examined had symptoms developing initially in the vaccinated arm, but this was not a consistent finding in later cases. Only 5 of the 23 children (22 percent) had objective findings, generally characterized by swollen joints, occasional tenderness, and in one case some limitation of motion because of pain. In no case was redness or heat of an involved joint observed. Detailed neurological examinations, which included testing for mental status, cranial nerves, deep tendon reflexes, motor and sensory status, cerebellar function and pathologic reflexes, were all essentially normal.

Except for pain and paresthesia of an involved extremity, other symptoms were characteristically lacking. Specifically, there were rare or no reports of headache, fever, chills, anorexia, vomiting, pharyngitis, cough, coryza, conjunctivitis,

TABLE 1.—*Selected Characteristics of Patients with Reported Post-Rubella Immunization Reactions (San Luis Obispo County, 1970)*

Case	Age	Sex	Days to Onset of Symptoms	Duration	Predominant Symptom Complex*	Objective Findings**
1	6	M	35	9	A+N	—
2	6	F	26	26	A+N	tender wrist
3	7	F	25	27	A+N	—
4	8	M	31	24	A+N	—
5	6	M	31	25	A+N	—
6	5	M	28	18	A	—
7	10	M	28	18	A	—
8	6	F	21	17	N	—
9	6	M	39	23	A+N	—
10	7	F	35	22	A+N	swollen tender hand
11	6	F	45	17	A+N	—
12	5	F	31	8	A	—
13	9	F	38	9	A+N	—
14	8	M	40	10	A	—
15	5	M	36	19	A+N	swollen tender wrist
16	6	M	54	8	A+N	—
17	6	F	39	10	A	—
18	5	F	39	15	A	—
19	8	F	38	4	A	—
20	8	M	38	18	A	knee kept flexed at 160°, pain if moved
21	5	F	39	18	A+N	—
22	5	M	30	18	A	swollen wrist, knee
23	5	F	30	19	A+N	—

\*"A"=Arthritis or arthralgia, as denoted by pain.

"N"=neuritis or neuralgia, as denoted by paresthesia (tingling sensation, "pins and needles", "sleeping" sensation, numbness, etc.).

Wherever "pain" was described, "A" was arbitrarily chosen though this symptom too might actually have been representative of a peripheral neuritis.

\*\*Objective findings as noted by parents, attending physicians, or the investigators.

adenopathy, rash, myalgia, altered sensorium, speech impairment, convulsions, incoordination or sensory deficit. Motor deficits, when reported, were considered secondary to pain or tenderness by the child or his parents. The pain showed a characteristic and peculiar diurnal pattern. Frequently associated with a tingling sensation, the pain in an involved extremity (most often at the elbow and distally) awakened the child every morning from a sound sleep and persisted several hours. By late morning or early afternoon, symptoms ceased. Typically, but not always, the patient then remained asymptomatic for the rest of the day, including bedtime, only to be awakened again during the early morning hours on subsequent days. All of the symptoms were self-limited and few required symptomatic treatment.

### Case Histories

Two case histories are described which exhibit the full gamut of musculoskeletal-neurologic complaints encountered. The first depicts

mild, single extremity involvement with a blend of pain and paresthesia suggestive of carpal-tunnel syndrome; the second, widespread and severe involvement with paresthesia (only) in one extremity and pain (only) in others.

Case 10. A seven-year-old girl was reportedly free of any past history of musculoskeletal symptoms. She was inoculated without any local reaction at the deltoid region of the right arm, but 35 days later began to complain of her right wrist hurting on flexion and of her right hand falling asleep. She awoke about twice each night with the same complaints. Her hand was reported to be visibly swollen at such times. Her physician, too, noted tenderness and swelling but there was no redness or local heat. This girl had no problem going to sleep and was generally free of complaints during the daytime except for transient pain in the right wrist. At these times she tended to splint her wrist to avoid pain. She had no other symptoms and her daily routine was otherwise unchanged. Symp-



toms lasted 22 days. When seen (by H.K.) during an asymptomatic interval, physical examination was entirely normal, including the right wrist and hand.

Case 9. A six-year-old boy was inoculated in the deltoid region of the left arm without immediate untoward effect. Thirty-nine days later he began to complain of pain in both popliteal areas. The pain typically awakened him from sleep and caused him to crawl about upon getting out of bed. Pain on straightening his legs was severe in the mornings but gradually abated and by noon he was on his feet, asymptomatic, and running about without any complaints. On the third day of illness, paresthesias alone were reported at, and distal to, his left elbow. Detailed questioning elicited no further complaints. No abnormal objective findings were noted by the mother nor by one of us (S.B.W.) who carried out a complete neurological and musculoskeletal examination. Symptoms fully cleared by the 23rd day.

### Laboratory Studies

Throat swabs were taken from nine children who were symptomatic and two yielded rubella virus in RK13 (rabbit kidney cell) cultures (cases No. 5 and 9). The specimen from case No. 5 was taken on the 8th day of symptoms, 38 days after immunization; that from No. 9 on the 4th day of symptoms, 43 days after immunization. Blood specimens were obtained at the same time from eight of the nine children, all more than one month following immunization. Rubella antibody was present in all sera, demonstrated by hemagglutination-inhibition (HI) and indirect fluorescent antibody (FA) tests; HI antibody titers ranged from 1:8 to 1:64 and FA antibody titers from 1:32-1:256. Severe hemolysis due to freezing of the blood specimens during shipment may have impaired the HI test results.

### Telephone Survey

As a control group, a total of 157 families, with 245 children from kindergarten through the fourth grade who did not receive rubella vaccine in the school program, were contacted by telephone and questioned in the same manner as those in the vaccinated group. Only one child had specific complaints of the type which were

recorded for this survey. She was a six-year-old girl with complaint of tingling sensations in her foot which lasted for two to three days. No other specific complaints of arthritis, arthralgia or paresthesia were elicited from the control group.

A total of 249 families with 414 vaccinated children were questioned by telephone, and 32 instances of symptoms possibly related to the vaccine were reported. Two children had a history of slight fever and a rash about two weeks after immunization. The other 30 recorded reactions ranged from mild arthralgia or paresthesia of an arm or leg to cases of arthritis. Further analysis and discussion concerns the latter 30 cases.

Typically, symptoms were prominent mainly during the early morning hours and generally were not bothersome later in the day, except in the cases of arthritis. In about half of the cases, paresthesia was a prominent if not the major complaint. Only seven children were reported to have had arthritic symptoms consisting primarily of joint swelling. Onset of reactions ranged from one to two weeks after immunization to over eight weeks, with most reactions occurring between the third and fifth weeks.

Table 2 presents these cases by age and sex. The overall rate of arthritis, arthralgia or paresthesia in the inoculated group was 7.2 percent. The rate in girls was almost double that for boys and the rate in five-to six-year-old children was almost double that of the older children. This age distribution was consistent for both sexes. Table 3 presents the duration of symptoms by sex. It can be seen that most reactions lasted two weeks or less but there was a pronounced difference between the sexes. Almost half of the reactions in girls lasted only two or three days, whereas only one of the reactions in boys was so brief. A sex difference was also observed in the severity of symptoms as five of the eleven boys but only three of the nineteen girls had symptoms severe enough to require medical attention.

### Discussion

In women with natural rubella, symptoms of arthralgia, arthritis or paresthesia have been frequently reported, but these complications have been thought rare in children.<sup>3</sup> These

**TABLE 2.—Reactions\* to Rubella Vaccine by Age and Sex San Luis Obispo Telephone Survey, July-August, 1970**

Age	Boys	No. of Reactions	Rate Per 100	Girls	No. of Reactions	Rate Per 100	Total	No. of Reactions	Rate Per 100
5-6 years	56	6	10.7	55	9	16.4	111	15	13.5
7-8 years	84	3	3.6	94	6	6.4	178	9	5.1
9-11 years	69	2	2.9	56	4	7.1	125	6	4.8
Totals	209	11	5.3	205	19	9.3	414	30	7.2

\* Arthritis, arthralgia and paresthesia.

**TABLE 3.—Duration of Vaccine Reactions by Sex (San Luis Obispo Telephone Survey, July-August, 1970)**

Duration	Boys	Girls	Total
1-3 days	1	9	10
4-6 days	2	4	6
1-2 weeks	3	2	5
3-4 weeks	2	3	5
>4 weeks	3	1	4
Totals	11	19	30

symptoms have now also been reported in women and in children following inoculation with live attenuated rubella vaccines. The dog kidney-derived vaccine used in this program has been associated with greater frequency of these reactions<sup>2,4</sup> and also has been shown to evoke a higher antibody response compared with other rubella vaccines.<sup>4</sup> It is possible that a higher rate of reactions is directly correlated with the amount of antigenic stimulus provided by each of the rubella vaccines. Further comparative data are now being compiled for all of the currently available rubella vaccines by the Center for Disease Control, Atlanta, Georgia.

In many field studies of rubella vaccine in children before the vaccine was licensed, only mild and very transient arthralgia or arthritis was reported in a small proportion of children. However, as the period of follow-up in those studies was only 25 to 30 days after immunization, the later reactions such as those observed in the San Luis Obispo program would have been missed. The high frequency of reactions in children reported in the present study raises question as to whether the full extent of these

complications following natural rubella in children has not been recognized or whether these reactions are a far more frequent complication of the attenuated dog kidney vaccine virus than of natural infection.

Fry et al,<sup>5</sup> in a study of a rubella outbreak in England, reported arthritis as a complication in 11 out of 74 adults but they were not able to document this reaction in any of 285 children. However, it is conceivable that most of these complications could have been overlooked, since they are difficult to differentiate from the almost accepted aches and pains of an active child, especially when the symptoms are mild, of short duration and of delayed onset. In women these complications to the natural disease usually begin several days after appearance of the rash but they can occur as early as one week before to several weeks after the rash begins.<sup>3</sup> These reactions in women have been reported to occur most frequently 12 to 22 days after rubella vaccine, which coincides with the usual period of vaccine virus shedding. Most of the vaccine reactions in children observed in our study did not occur until about one month after immunization. Whether this delayed onset of symptoms is part of the natural pathogenesis of rubella in children or is peculiar to infections with the vaccine virus will have to be determined by detailed studies of the natural disease in children followed prospectively from the date of diagnosis. We are planning such studies. These studies should also determine whether the extent and characteristics (such as the predominant unilateral involvement of an upper extremity) of the observed vaccine reactions are similar to those which occur after natural disease.

Although the opportunities of virus recovery in this investigation were limited to a single



throat swab from nine children, rubella virus was isolated from two of them. The two positive swabs were collected at 38 days and 43 days post-vaccination. If multiple swabs on consecutive days during the symptomatic period had been obtained, the number of virus recoveries might have been increased, and possibly even longer intervals of post-vaccinal virus shedding would have been noted.

In our study we were impressed that the chief complaint was primarily that of paresthesia rather than the accompanying pain. Cooper et al<sup>1</sup> in their studies of transient arthritis after rubella vaccine stated that "paresthesia often accompanies and may outlast a joint symptom." They also noted that in some women paresthesia was a prominent feature and at times more disturbing and persistent than pain. Similar peripheral neuritis-like symptoms may complicate natural rubella in women<sup>6-9</sup> although this has not been widely recognized.

The pathogenesis of these reactions is not known, but arthritis has also been reported as a natural complication of other common viral or presumed viral diseases.<sup>10</sup> In documented outbreaks of erythema infectiosum a transient arthralgia and arthritis has been observed.<sup>11</sup> Arthritis as a complication of mumps may be more common than is currently recognized, and it has been suggested that this syndrome, like other complications of mumps, might occur without parotitis.<sup>12</sup> Whether arthritis occurs after mumps vaccine has not been reported but the question should be investigated. It is possible that arthritis associated with these common viruses may well account for many of the vague "growing pains" reported by children.

In contrast to the finding in immunized women of a direct relationship between increasing age and the frequency of reactions,<sup>1</sup> an opposite trend was observed in our study in that the youngest children had the highest attack rates. This finding might be accounted for by the decreasing susceptibility to rubella with increasing age, due to acquired immunity from past natural infection. It has been shown that these vaccine reactions are not observed in women<sup>13</sup> nor in children<sup>4</sup> who have had past experience with natural rubella. We found an almost 2 to 1 ratio of girls to boys for these reactions in the telephone survey. In another field survey, a 4 to 1

female to male ratio was found.<sup>4</sup> Although boys were involved less frequently, their symptoms tended to be more severe. This would explain the almost equal male to female ratio of the initially reported cases which were referred to our attention by physicians. The reasons for these sex differences are not known.

The primary approach for the control of rubella in this country is to immunize children to prevent the spread of rubella in the community. To date about 14 million children have already received rubella vaccine through public programs alone.<sup>14</sup> Vaccine reactions in children may hinder the rubella control program, as it was previously thought that the rubella vaccines were free of any appreciable side effects in children. On the other hand it should be emphasized that most of these reactions have been mild and self-limited. Very few children have had significant limitation of their normal activities while symptomatic, and these reactions have not been associated with any sequelae such as joint damage or rheumatoid arthritis.<sup>15</sup> In addition, most of the public programs to date have used rubella vaccines which have not been associated with as high a frequency of reactions as the dog kidney-derived vaccine. However, the extent and nature of these vaccine reactions in children should be brought to the attention of medical groups and the general public in the planning and implementation of rubella immunization programs.

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# Methylmercury Poisoning

## An Assessment of the Sportfish Hazard in California

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■ *A quantitative assessment of the methylmercury risk in California entails measurement of the contamination distribution, the probability of methylmercury intake and knowledge of the toxicological properties of methylmercury. This article reviews the scientific basis for the California State Task Force's decision to warn the public against excessive consumption of sport fish contaminated by methylmercury.*

IN OCTOBER 1970 a California State Task Force on mercury and health with one of us (E.K.) as chairman officially recommended to the California public that, because of the health hazards associated with methylmercury contamination, consumption of sport fish be limited to one meal a week. The three species of sport fish named as being highly contaminated were striped bass, catfish and sturgeon. Furthermore, pregnant women were warned not to eat any sport fish. (This warning is now being extended to any woman of child-bearing age who has a chance of becoming pregnant.) The intent of this paper is to convey to California's physicians and related health groups the rationale for the Task Force's recommendation.<sup>1</sup>

### Mercury Toxicity

Mercurial compounds differ considerably in their toxicological properties.<sup>2,3</sup> Excessive occupational exposure to metallic mercury vapor and dusts of inorganic mercury salts can result in neurological and renal damage. In contrast, organomercurial diuretic agents, when administered

properly, rarely exert any effect other than diuresis. Other widely used organomercurial compounds such as merbromin (Mercurochrome),<sup>4</sup> phenylmercuric acetate and alkoxymercuric salts can produce allergic contact dermatitis but seldom cause systemic toxicity. The health threat from mercury contamination in the environment arises not from the above-mentioned groups of mercurial compounds but from the short-chain alkylmercury compounds, viz. methylmercury.

Methylmercury\* damages the brain.<sup>5,6</sup> The initial symptoms observed in man are numbness and tingling of the lips, hands and feet. In more severe cases the sensory changes prelude the concentric loss of visual fields followed by ataxia of cerebellar origin, convulsions, coma and death. In fatal cases histopathological studies show degenerative changes in the granular layer of the cerebellum and in the calcarine cortex of the brain. The clinical course is of prolonged duration and the damage is usually permanent since the lesions result from loss of neural tissue. Chelating agents are ineffective antidotes and may aggravate the disease.<sup>7</sup>

The fetal brain may be especially sensitive to the toxic effects of methylmercury. Twenty-two

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\*CH<sub>3</sub>Hg<sup>+</sup>, the anion does not change the toxicological properties.



cases of cerebral palsied and neurologically-dis-eased infants were observed out of approximately 400 live births in the Minamata Bay region of Japan<sup>3,8</sup> (Minamata Bay is the area where excessive consumption of methylmercury-contaminated fish and shellfish resulted in 46 deaths out of 121 cases). The normal incidence of cerebral palsy in the United States averages 0.15 to 0.20 percent of live births.<sup>9</sup> In animal studies, methylmercury selectively accumulates in fetal tissue.<sup>3</sup> Genetic studies show that methylmercury is more potent than colchicine in inhibiting mitosis.<sup>10</sup> The fetotoxic dose in man is not known.

### Sources of Exposure

Alkyl and aryl mercury compounds have been used as fungicides since the 1930s, and the earlier reports of poisoning dealt with inhalation of the fungicide during the processes of manufacture and distribution.<sup>2</sup> Mass poisoning has occurred in countries where treated seeds were accidentally used for food.<sup>11</sup> Recently a family in New Mexico was stricken after eating hogs that had been fed seeds treated with a methylmercury fungicide.<sup>12</sup> In many countries the use of alkylmercury fungicides is being curtailed and the agent replaced with safer compounds. In the United States, however, legal maneuvers have stalled the de-registration of methylmercury fungicides and, consequently, most of the seed grain planted in California is still being treated with methylmercury compounds.

More serious, because it is less easy to prevent, is methylmercury poisoning that may result from consumption of contaminated fish. Methylmercury reaches the fish in an indirect manner.<sup>13</sup> Large amounts of inorganic or phenylmercury compounds are commonly discharged into natural water bodies in connection with a number of industrial operations (mercury and gold mining, paper pulp processing and chlorine-alkali factories are examples). Until very recently industrial and sanitary engineers assumed that this mercury was inert since the discharged mercury compounds were relatively insoluble and sampling showed insignificant traces of mercury in the water. Swedish workers, however, have shown that bacterial species, commonly found in the bottom sediment of fresh and salt water bodies, synthesize methylmercury from inorganic mercury. Methylmercury is then concentrated as successive rungs of biologic food chains are ascended, so

that in contaminated waters the larger fish may contain high tissue levels of methylmercury. Cooking does not remove the methylmercury in fish.<sup>14</sup>

In California there is an abundance of mercury mines, of industrial users of mercury, and of enclosed areas of fresh and tidal water. Sampling programs which were started by several agencies in 1970 revealed that 35 to 50 percent of the fish caught in scattered locations throughout the Sacramento and San Joaquin River drainage (and several other lakes, rivers and bays as well) have mercury levels exceeding 0.5 mg per kg of fish. The unofficial federal tolerance limit for mercury in fish is 0.5 mg per kg. Of 43 striped bass weighing over 4 pounds that were analyzed for mercury, all had more than 0.5 mg per kg. None of the samples analyzed, however, exceeded 2 mg per kg.

### Assessment of the Hazard

At what levels of methylmercury is the fish safe for human consumption? Using a probabilistic approach Spear<sup>15</sup> and one of us (E.W.), at the University of California at Berkeley, have simulated patterns of methylmercury intake in a computer and calculated the expected body levels of methylmercury for different probability distributions of intake and contamination. For fish contaminated with a median level of 0.5 mg per kg, 5 percent of the fish-consuming population would have maximum body levels of methylmercury greater than 2.9 mg if they ate fish once every 12 days and greater than 6.0 mg if they ate fish once every four days. The lowest body level observed in 12 fatally poisoned Japanese adults<sup>5</sup> was about 50 mg (average 129 mg, range 50 to 273 mg). The Swedish authorities, basing their calculations mainly on the Japanese data, have estimated the neurotoxic dose in man to be 60 to 70 mg.<sup>16</sup> If we allow a safety factor of 10 for individual variability in excretion and susceptibility, it can be seen that excessive consumption of fish will entail certain risks. Of special concern are low-income groups living in the Sacramento Delta and members of fishing clubs. These people catch and consume large quantities of striped bass and catfish, the species containing the highest levels of mercury.

Brain cells do not regenerate. The absence of gross, clinical signs of methylmercury poisoning

does not mean that neurons are not being damaged by low levels of methylmercury. The capacity of a functional reservoir of neurons is not known. For irreversibly-acting neurotoxins the threshold concept may be a mirage.

## Future Areas of Investigation

With due consideration to the funds available, the following areas of investigation are being jointly planned by the University of California School of Public Health at Berkeley and by the California State Department of Public Health:

- An assessment of the health hazards from mercury contamination of foodstuffs other than sport fish,
- An epidemiological survey of exposed populations to determine if methylmercury exposure *in utero* is related to certain congenital neurological disorders, and
- The establishment of a long-term environmental surveillance program to control health hazards.

For the practicing physician we hope to have available an analytical method for methylmercury determinations<sup>17</sup> in hair, blood or urine, so that risks from poisoning can be readily assessed. Additional information will be communicated to the public when the data are collected and evaluated.

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## TESTING FOR SENSORY PARESIS WITH VOCAL CORD PARALYSIS

"For a long time I never tested for sensory paresis or paralysis when I saw a patient with a paralyzed vocal cord. But a simple test is to dress a curved laryngeal applicator with cotton and test the sensation of the epiglottis, the aryepiglottic folds, and the false and true cords. . . . Care must be taken not to touch the base of the tongue during this procedure since we want to test primarily the tenth nerve and not the ninth. We test first one side and then the other; and we will find not only unilateral but sometimes bilateral lesions."

—DAVID W. BREWER, M.D., Syracuse

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# The Clinical Physiology of Calcium Homeostasis, Parathyroid Hormone, and Calcitonin

## Part I

CHARLES R. KLEEMAN, M.D., SHAUL G. MASSRY, M.D., AND  
JACK W. COBURN, M.D., *Los Angeles*

THE CONCENTRATIONS OF CALCIUM ion ( $\text{Ca}^{++}$ ) in the intracellular and extracellular fluids and in cellular and sub-cellular membranes are maintained with remarkable constancy, a reflection of the critical role of  $\text{Ca}^{++}$  in many fundamental biologic processes. The integrity, electrical properties, and permeability of these cellular and sub-cellular structures are critically dependent on calcium ion. Membranes depleted of calcium ion become increasingly porous and lose their selective permeability characteristics. Calcium ion is also an essential coupling factor or "biologic transducer" in the depolarization of cell membranes and conversion of electrical activity into contraction of skeletal, cardiac, and smooth muscles and in stimulus secretion coupling for glands of internal and external secretion. Calcium ion also plays an important role in the process of blood coagulation and in the activation of many intracellular enzyme systems.

In this report, the homeostatic regulation of  $\text{Ca}^{++}$  concentration of the body fluids and the role of the skeleton in this regulation will be dis-

cussed; this will lay the foundation upon which a discussion of the clinical physiology of parathyroid hormone and calcitonin is built. The contribution of the other major divalent ions, magnesium and phosphorus, will also be presented.

### *Physicochemical State of Calcium, Magnesium and Inorganic Phosphorus in the Plasma*

Total plasma calcium is composed of two major fractions: (1) The protein-bound (non-diffusible or non-ultrafilterable) fraction which constitutes  $40 \pm 5\%$  of the total plasma calcium concentration, and (2) The non-protein-bound (diffusible or ultrafilterable) fraction which constitutes  $60 \pm 5\%$  of the total calcium level;  $6 \pm 5\%$  of the diffusible fraction is present in the form of complexed calcium, and  $94 \pm 5\%$  is in the form of calcium ion.<sup>1</sup> Therefore, the concentration of  $\text{Ca}^{++}$  in the plasma is about 50 percent of the total plasma level, and it is this concentration of  $\text{Ca}^{++}$  which is critically controlled by the homeostatic mechanisms.

The relationship between calcium ion and the concentration of protein in the blood is represented by a simple mass action expression:

$$\frac{(\text{Ca}^{++}) (\text{Protein})}{\text{Calcium Protein}} = K \quad \text{where protein} = \text{concentration of plasma protein, primarily albumin.}$$

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Since  $K$  is constant, the numerator and denominator must change proportionately in any physiologic or pathologic state. A change in the concentration of total plasma calcium will occur following a change in the concentration of serum proteins or alterations in their binding properties and after a primary change in the concentration of calcium ion. A fall in serum albumin reduces the proteinate and the calcium proteinate proportionately, resulting in a fall in total plasma calcium level with the free calcium ion concentration remaining normal. Therefore the diffusible fraction will constitute a larger portion of the total plasma calcium. A decrease in the concentration of serum albumin by 1 gram per 100 ml is usually associated with a fall of 1 mg per 100 ml in the concentration of total serum calcium.

Such hypocalcemia represents no basic disorder in the regulation of the concentration of calcium ion. It is apparent that a proper interpretation of a total plasma calcium cannot be made without a knowledge of simultaneous concentration of plasma albumin. Since only a small amount of calcium is bound to globulin, it is unusual to see a change in the total concentration of plasma calcium as a result of alteration in the level of plasma globulin. However, on rare occasions, when the globulin concentration in the plasma is extremely high (greater than 6 grams per 100 ml), a mild-to-moderate hypercalcemia may be seen due to an elevation of the globulin-bound calcium. In these circumstances, the concentration of free calcium ion is normal, and, therefore, this kind of hypercalcemia would not necessitate specific treatment. Therefore, in patients with elevation in total serum calcium and hyperglobulinemia, one should always determine the level of the diffusible fraction of serum calcium in order to differentiate between true hypercalcemia (elevation in the  $\text{Ca}^{++}$  concentration) and hypercalcemia secondary to increased binding of calcium by the high levels of globulins.

The concentration of plasma sodium may also affect the binding of calcium by serum albumin, resulting in changes in total serum calcium concentration. Walser<sup>2</sup> demonstrated that severe hypo- and hypernatremia (less than 120 mEq per liter and greater than 155 mEq per liter) could

cause a predictable change in total plasma calcium concentration, due to a change in the calcium binding property of plasma proteins. Hyponatremia caused an increase in protein-bound calcium and therefore slight hypercalcemia, while hypernatremia caused a decrease in the protein-bound calcium and therefore slight hypocalcemia. In neither case was the concentration of  $\text{Ca}^{++}$  altered. If a tourniquet is left on the arm for 2 to 3 minutes before obtaining a blood specimen, transudation of protein-free fluid out of the capillary blood will result in concentration of the plasma proteins and subsequently lead to a rise in the protein-bound calcium;<sup>3</sup> this phenomenon might cause an elevation of 0.5 to 1.5 mg per 100 ml in the level of total serum calcium. Therefore, every effort should be made to obtain a blood specimen for the measurement of total serum calcium from free-flowing blood.

If for some physiological or pathological reason the concentration of free calcium ion changes, the calcium proteinate component will also change proportionately; this will result in a proportionate change in the level of total, bound, and diffusible calcium. Therefore, in all hypo- and hypercalcemic disorders due to primary changes in the concentration of calcium ion, the ratio of the diffusible to non-diffusible fractions remains constant, or normal. This is in contrast to altered ratios between the diffusible and bound fractions of calcium in cases where the change in total serum calcium is due to alterations in the concentrations of serum protein or in their binding properties.

In summary, the concentration of total plasma calcium is determined by the mass action relationship of  $\text{Ca}^{++}$  with the protein, while the concentration of  $\text{Ca}^{++}$  is controlled by the dynamic equilibrium between the metabolically active component of the skeleton and the extracellular fluid bathing this component.

The normal concentration of magnesium in the plasma is between 1.7 and 2.0 mg/100 ml; magnesium in the plasma is also present in two forms, a diffusible and a non-diffusible fraction. As in the case of calcium, the non-diffusible fraction is bound to proteins, and the relationship between the diffusible and the non-diffusible fraction follows the simple mass action equilibrium. The normal concentration of the inorganic phosphate in plasma of adults is 2.5 to 4.5 mg per 100



ml; it usually varies with age and sex<sup>4</sup> (Chart 1). The level of plasma phosphorus is 1 mg per 100 ml higher in children below the age of puberty; this higher level is possibly due to increased action of growth hormone, which elevates the

plasma phosphorus. For practical purposes one can consider that all of the inorganic phosphorus is in diffusible form. At the pH of the body fluid, 80 percent of inorganic phosphorus is in the form of  $\text{HPO}_4$  and 20 percent in the form of  $\text{H}_2\text{PO}_4$ .

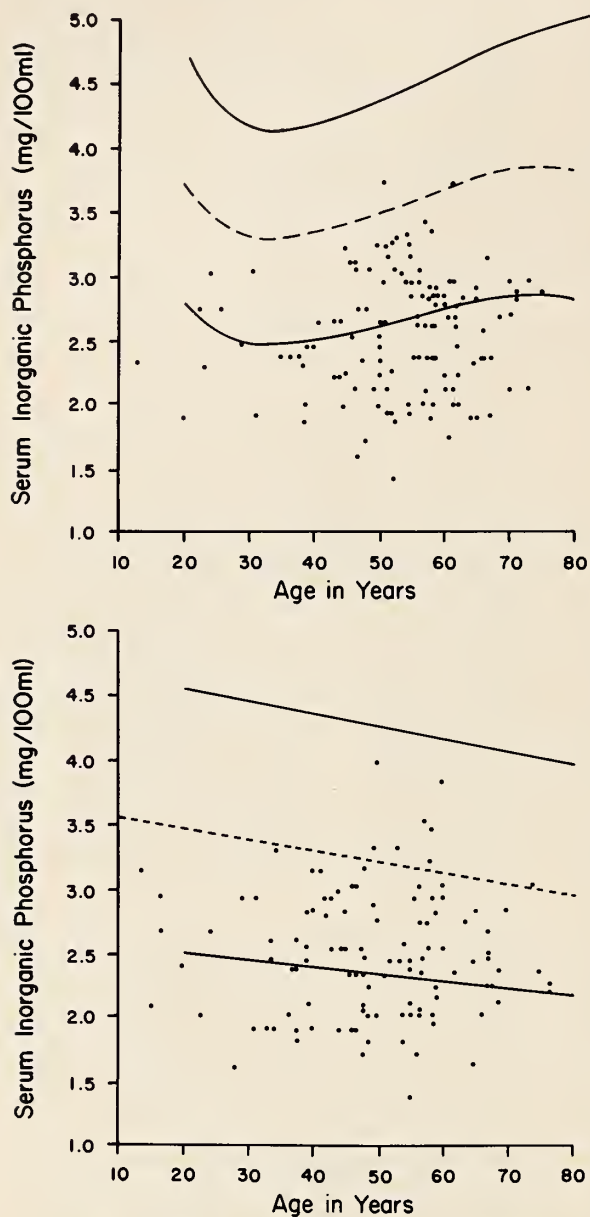


Chart 1.—Mean preoperative serum phosphorus values in patients with primary hyperparathyroidism; upper, men; lower, women. Broken lines represent normal mean expressed as regression with age; solid lines represent 2.5 and 97.5 percentile limits of normal distribution. Each dot represents the mean preoperative value for a patient. Individual preoperative values would show a larger proportion of patients having one or more values within the normal range. (Redrawn from Keating, F. R., Jr.)

## Homeostatic Regulation of the Concentration of Calcium Ion Of the Plasma

The concentration of calcium ion in the plasma is maintained constant despite pronounced changes in external balance of calcium. If the fundamental factors regulating the calcium content of the body fluid are intact, a patient may lose 25 to 30 percent of the total body content of calcium without a change in the concentration of calcium ion of the plasma. Also, after the administration of a large oral or parenteral calcium load, serum calcium rapidly returns to normal after a brief period of disequilibrium. This rapid buffering of hypo- or hypercalcemic stress is illustrated in Chart 2.<sup>5</sup> This buffering capacity is fundamentally due to the dynamic equilibrium between the metabolically active part of the skeleton and the extracellular fluids. While variations in intestinal absorption and renal excretion of calcium will contribute to the concentration of calcium ion in the plasma, most clinically known hyper- or hypocalcemic disorders are not due,

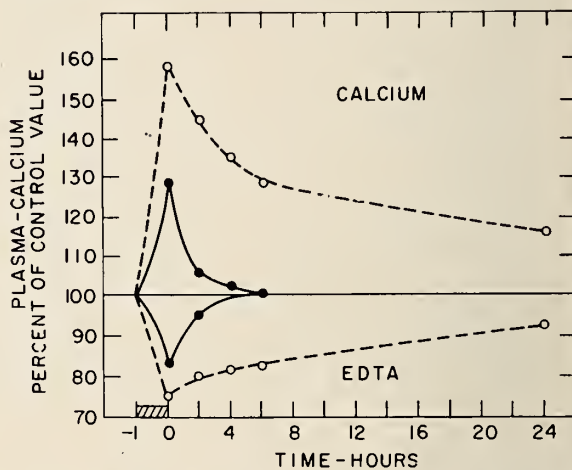


Chart 2.—The change in plasma calcium concentration induced by calcium or EDTA infusions into dogs before (closed circles) and after (open circles) thyroparathyroidectomy. The normal animal can rapidly restore the calcium concentration to normal; the thyroparathyroidectomized animal is unable to compensate quickly for either the hypocalcemia or hypercalcemia. (Redrawn by Potts & Deftos from Sanderson, P.H., et al.)

TABLE 1.—Distribution of Calcium (Ca), Phosphorus (P) and Magnesium (Mg) in Body Tissues\*

	Total body composition (gm./kg. fat free tissue)		
	Ca 20-25	P 11-14	Mg 0.5
Relative Distribution (Percent)			
Specific tissue			
Skeleton .....	99	85	66
Muscle .....	0.3	6	19
Other tissues .....	0.7	9	12

\*Modified from S. M. Krane. (From Potts & Deftos<sup>6</sup>)

*per se*, to an abnormality in the intestinal absorption or the renal excretion of calcium. Therefore, the basic cause of almost all physiologic and pathologic changes in the concentration of calcium ion in the plasma is an alteration in dynamic equilibrium between the bone and the extracellular fluid.

### The Skeleton and the Homeostatic Control of the Concentration of Calcium Ion in the Plasma

The total calcium content of normal adult humans is 20 to 25 grams per kilogram of fat-free tissue, with 99 percent in the skeleton (Table 1)<sup>6</sup> and the remainder in the extracellular fluid. Studies utilizing calcium-45 and calcium-47

showed that 1 percent of skeletal calcium is freely exchangeable with that in the extracellular fluid, and these fractions constitute the miscible pool of calcium;<sup>6</sup> and a dynamic equilibrium is maintained between these two components of the miscible pool. The continuous bone remodeling involving the process of bone resorption and accretion, brought about by the metabolic activity of the skeleton, guarantees the maintenance of the readily exchangeable component.

To understand clearly the role of the different factors which may control or effect the processes of bone resorption and accretion, it is essential to visualize the functional anatomy of the skeleton. Figure 1<sup>6</sup> portrays the structure of mature bone and demonstrates the pattern of the vascular supply which is fundamental to support the metabolic functions of the skeleton.

Although Havers described in 1691 the canal which bears his name, he failed to describe the concentric lamellae around these vascular canals; therefore the term *osteon* rather than Haversian system may be used more appropriately to describe the morphologic unit of compact bone. Cooper, Milgram, and Robinson<sup>7</sup> have defined an osteon as "an irregular, branching and anastomos-

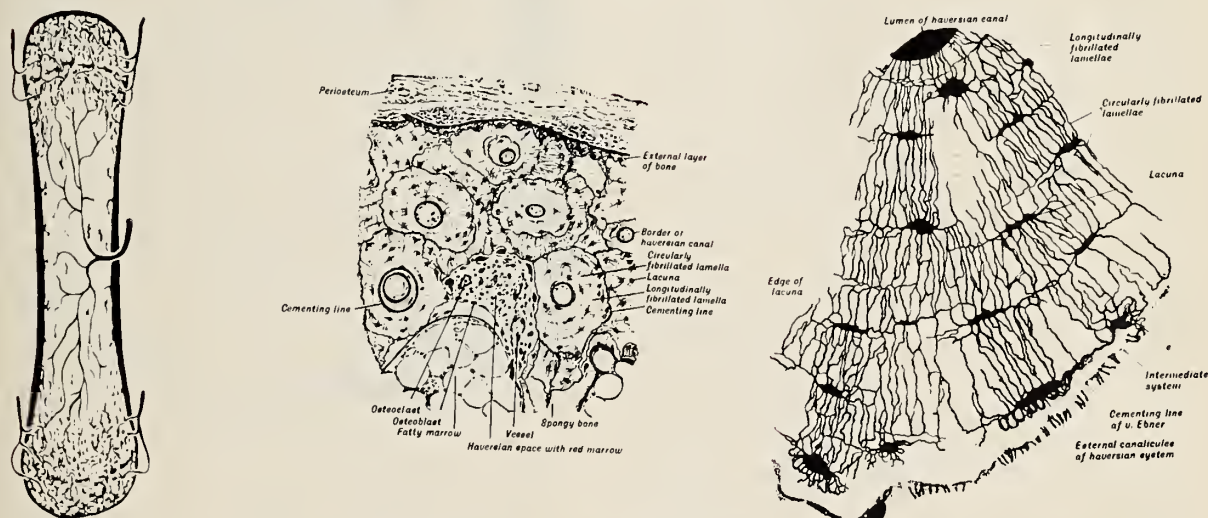


Figure 1.—Composite figure (left to right) of vascular supply of fully developed bone (phalange); a histologic cross-section of same illustrating cellular elements and details of numerous osteons with concentric lamellae, lacunae and central Haversian canals; and a higher magnification of a cross-section of a Haversian system. In the latter (magnification 520) the cavities and canalicules are filled with a dye which illustrates the connection via canalicules of the Haversian system and the lacunae (which *in vivo* contain osteocytes). (After A. A. Maximow. From Bloom, W., and Fawcett, D. W.: A Textbook of Histology, 9th ed., 1968, as reproduced from Ref. 6.)



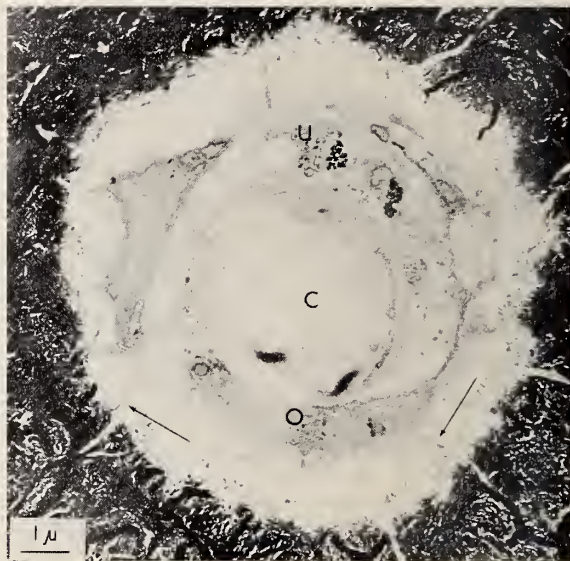
ing cylinder composed of a more or less centrally placed cell-containing neurovascular canal surrounded by concentric, cell-permeated lamellae of bone matrix." They expand upon the definition: "For descriptive purposes, osteons and their enclosed Haversian canals can be divided into three types: developing, mature and resorbing, depending on the types of cell in the canal and the variations in the matrix around the canal. These categories cannot be sharply delineated since there are gradation of osteons, from the early developing to the mature; nevertheless, in any one ultra-thin section, one of these types predominates even though a different type of activity might be seen at another level of the same osteon." At one level of the osteon, usually near the periphery of the Haversian canal, osteoclasts are the predominant cells and bone resorption is the prevailing process. At another level the predominant cell may be osteoblasts, which are actively involved in the formation and deposition of collagen fibrils, in and around which mineralization is proceeding (Figure 2). Resorption of mineral and matrix may also occur around the osteocytes in their lacunae.

The cellular relationships around a capillary in Haversian canal, as visualized by electronmicroscopy, are shown in Figure 3. Osteoblasts and their primitive precursors, mesenchymal cells, form a syncytial lining between the capillaries and unmineralized (collagen) and mineralized matrix (mature bone). In more immature osteons, osteoblasts appear active and are filled with rough endoplasmic reticulum, suggesting that they actively synthesize protein. Indeed, the quantity of collagen fibers seen around them is good evidence for such an activity (Figures 2 and 3). Cytoplasmic processes of active osteoblasts extend out of the Haversian canal into layers of collagen and mineralized matrix by way of numerous canaliculi, reaching toward the processes of adjacent osteocytes. As matrix formation and mineralization continues, the active osteoblasts become encircled, first with layers of unmineralized and subsequently with mineralized matrix; they then become osteocytes lying within their lacunae. (Figure 2).

**O**steoclasts, which are large multinucleated cells with abundant mitochondria containing dense granules of calcium-phosphate salts, are



**Figure 2.**—The edge of an Haversian canal in a developing osteon showing an osteoblast (O) being buried by matrix which is mineralizing, thereby converting the cell to an osteocyte. Mineral is deposited in relation to the collagen fibrils irrespective of their direction. In the fibrils cut in cross-section, it can be seen that the mineral is within the fibrils (arrow) (lead citrate).<sup>1</sup>



**Figure 3.**—Haversian canal in a developing osteon of a puppy. The central capillary (C) is composed of portions of several endothelial cells. The osteoblast (O) below the capillary contains abundant rough-surfaced endoplasmic reticulum. Osteoblast processes (arrows) leave the Haversian canal via canaliculi and extend into the surrounding matrix. The undifferentiated mesenchymal cells (U) contain dark clumps which probably represent glycogen. At the periphery of the canal irregular mineralization can be seen in relation to the white, negative images of collagen fibrils. The inner-most concentric mineralized lamellae surround the canal (lead citrate).<sup>1</sup>



seen along the edge of the Haversian canal in areas where bone resorption is active. These cells lack rough surface endoplasmic reticulum but contain smooth vesicles in their cytoplasm and have a ruffled border adjacent to the bone (Figure 4). Numerous bone crystals and remnants of collagen fibrils are seen between the cytoplasmic extensions of these cells.

The cells lining a mature Haversian canal appear to be inactive osteoblasts which are compressed against the walls of the mineralized matrix in the small space between the matrix and the Haversian capillary. These cells are extremely attenuated in places with the plasma membrane of one side of the cell in close contact to that of the other. There appear to be gaps between some of these cells, creating discontinuity in the cellular lining of the Haversian canal and allowing direct contact between extracellular or interstitial fluid and the fluid within the canaliculae and lacunae.

The crystal surfaces exposed to modified extracellular fluid along the walls of the lacunae, canaliculi and Haversian canals is immense; Robinson<sup>8</sup> estimated this to be 1500 to 5000 square meters in the average man. Bone crystal surfaces exposed in these areas could afford access to 3,120 square meters of surface on about 15.6 grams of bone crystals. Thus, an exchange of mineral ions may constantly occur via a water bridge which extends from the inside of the Haversian vessels to the crystal surfaces of bone on the walls of the Haversian canals, canaliculi, and lacunae.

In 1955, at the Ciba Foundation Symposium on Bone Structure and Metabolism, Dr. John E. Howard<sup>9</sup> made the following intuitive and perceptive statement: "... The bones have been shown, beyond reasonable doubt to be the site of operation for a buffer system which stabilizes the concentration of calcium in the body fluids. One conceives of the bone crystal as a gigantic pile of mineral materials, controlled locally by an active barrier; this barrier having an inherent or basic level of operation. The parathyroid hormone is one force which effects it and alters its basic rate. Structurally, the barrier could be a membrane derived from endosteal cells or their proliferatives; and, therefore, changes in its properties would be due to cellular activity of the bone cells. In this visualization the bone cell has been given still further duties—those of the por-

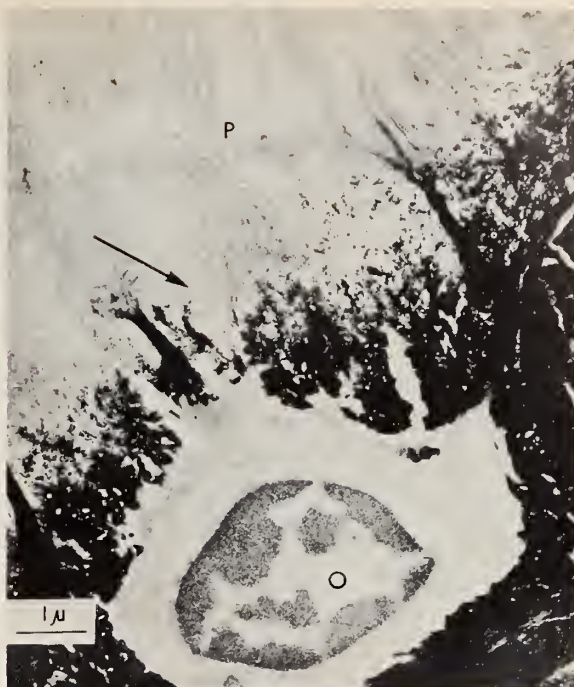


Figure 4.—In the upper portion of the micrograph the ruffled border of the osteoclast is seen. Between the cell processes (P) are numerous mineral crystals. Beneath the processes are portions of collagen fibrils (arrow) among which are many crystals. An osteocyte (O) is seen lying in its lacuna in the mineralized matrix (lead citrate).<sup>7</sup>

ter and the janitor, in addition to being the architect, the builder and the demolition squad of the skeleton mansion." Howard's hypothesis has gained increasing support and it seems probable that osteoblasts and certain osteoblast precursors constitute an effective active transport barrier that regulate the exchange of ions between bulk extracellular fluid and mineralizing bone collagen.<sup>8,10-13</sup>

On the bony side of the osteoblasts, there exists the bone extracellular fluid flowing within the canicular and periosteocytic lacunar spaces and directly associated with mineral-like tissues; the ionic concentrations of calcium and phosphate of this fluid are determined by the solubility product of hydroxyl apatite and the levels of these ions are approximately one-third as much as their concentrations in extracellular fluid.<sup>10,14</sup> On the other side of the osteoblasts there exist the central Haversian canal, capillary and bulk extracellular and interstitial fluids which have a divalent ion composition identical to that of the general body interstitial or bulk extracellular



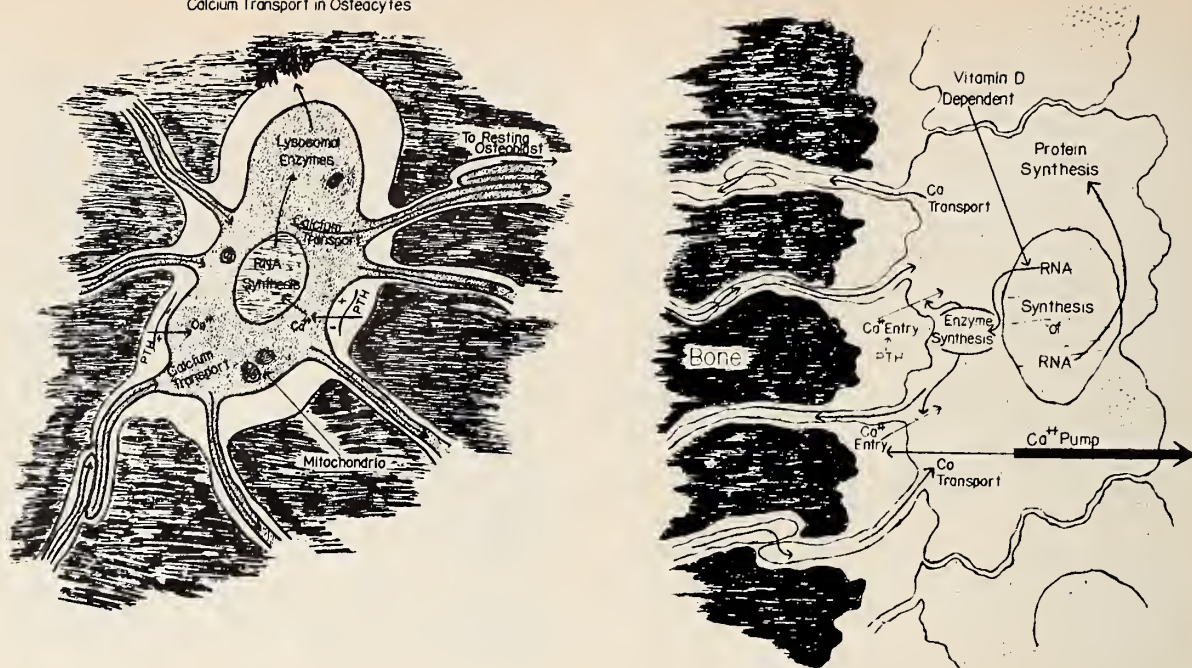


Figure 5.—Composite reproduction of diagrams from Talmage, R. V.<sup>10</sup> On the right, transcellular calcium transport through the “osteoblast” layer of bone is represented, while on the left is diagramed the osteocyte, “communicating” with the osteoblast through the canalicular system, with the various factors influencing calcium transport to and from the cell.

fluid. Thus, calcium and phosphate ions in bulk extracellular fluid may flow down their concentration gradients in the gaps (400 Å to 2 m $\mu$ ) between the osteoblastic lining cells (Figure 5). This provides a mechanism for inward movement of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  for mineralization of new matrix (bone accretion); thus, there is a continuous tendency for  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  to leave extracellular fluid and be deposited as new or growing crystals of hydroxyl apatite in or on the organic matrix of the skeleton. Calcium ion can also diffuse “downhill” into the lining cells for the intracellular  $\text{Ca}^{++}$  concentration of all cells is maintained at an extremely low level ( $10^{-7}$  to  $10^{-6}$  molar which is less than one-thousandth the concentration of  $\text{Ca}^{++}$  in extracellular fluid). This low intracellular  $\text{Ca}^{++}$  concentration is maintained by low membrane permeability and the presence of an active transport pump capable of removing  $\text{Ca}^{++}$  from the cell into the extracellular fluid surrounding it.<sup>10,11,15</sup> It has been suggested that the actual active transport pump in the osteoblast lies on the side of the cell facing the Haversian capillary and that this surface is also less permeable to the inward diffusion of cal-

cium ion.<sup>10</sup> Thus, there also may be net movement of large amounts of calcium ion by passive inward diffusion from bone through bone extracellular fluid into the cells lining the Haversian canal; from these cells calcium is actively transported into bulk extracellular space (Figure 5); control of this transport is determined by various hormonal and non-hormonal factors regulating the metabolic activity of these cells.

The osteocyte, which can produce large amounts of lactic acid and form considerable quantities of hydrolytic enzymes and collagenases, which play critical roles in mineral and matrix resorption, is also capable of active calcium transport.<sup>8,12</sup> During active osteocytic bone resorption (osteolysis),  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  ions are transported from the osteocytes to the osteoblasts along the protoplasmic extensions of these cells, which make contact within the canaliculi and in the fluid flowing in the lacunar-canalicular system (Figures 1 and 5). Thus, mechanisms are available whereby these ions may be delivered into the circulation from the depths of mature or fully mineralized bone. Osteolysis, rather than osteoclastic bone resorption, is considered by

many to be the primary metabolic activity of the skeleton responsible for maintaining the normal  $\text{Ca}^{++}$  concentration in the blood.<sup>6,10-13</sup> Although the osteoclast is also capable of causing very active bone resorption, its contribution to the normal control of blood  $\text{Ca}^{++}$  has recently been minimized.<sup>6,10,11,12,13</sup> Although parathyroid hormone affects the number and activity of osteoclasts, Talmage<sup>10,17</sup> has shown that this action of the hormone cannot satisfactorily explain the regulation of serum calcium levels by parathyroid hormone. However, the osteoclast is considered to have an important role in skeletal homeostasis or bone remodeling. Two clinical examples of hypocalcemia despite marked osteoclastic bone resorption are found in cases with osteitis fibrosa of renal osteodystrophy and occasionally in patients with classical pseudohypoparathyroidism.<sup>16</sup>

Neuman and Neuman<sup>14</sup> have shown that the mineral phase of inert bone mineral comes into equilibrium with  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  at an ion product of about one-third of that normally found in plasma and extracellular fluid; thus, there is supersaturation of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  in extracellular fluid with respect to bone mineral. In the absence of metabolic activity of bone cells or the cellular barrier interposed between bulk extracellular fluid and the mineralized matrix, the  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  concentrations in the plasma would rapidly fall as these ions are deposited in the skeleton. Therefore, the maintenance of normal  $\text{Ca}^{++}$  concentrations and, in part, the  $\text{PO}_4^-$  concentration in plasma are dependent upon the cellular processes of bone resorption and "uphill" transport of these ions against their physicochemical gradient. It is apparent that these processes must be continuous, and the importance of parathyroid hormone in their maintenance is clearly evident from the rapid fall in plasma  $\text{Ca}^{++}$  concentration which occurs when the parathyroid glands are removed.

#### *Hormonal and Non-Hormonal Regulators of Mineral Homeostasis*

When bone growth, *per se*, has ceased and a normal calcium and phosphorus balance is present in healthy adults, the urinary excretion of these ions is approximately equal to their net absorption from the gastrointestinal tract. Bone remodeling takes place at all times, and, therefore, there should be a continuous balance be-

tween the processes of bone accretion and bone resorption. Such a balance is brought about by several hormonal and non-hormonal factors which continuously regulate the activity of the osteoblasts, osteocytes and osteoclasts which are involved in these two processes. These factors include inorganic phosphate, calcium ion, magnesium ion, vitamin D, adrenal glucocorticoids, parathyroid hormone, and calcitonin.

*Inorganic Phosphate* ( $\text{PO}_4^-$ ). Experimental and clinical evidence indicates that inorganic phosphate plays an important role in calcium homeostasis and bone metabolism; the rate of net flux of calcium into and out of the skeleton under the influence of parathyroid hormone and calcitonin is intimately dependent on the level of inorganic phosphate bathing the internal and external environment of the metabolically active bone cells.

A positive external balance of inorganic phosphate or a rise in the concentration of this ion in the extracellular fluid shifts the skeletal dynamic equilibrium toward a net movement of calcium into the skeleton; this is associated with a fall in the concentration of  $\text{Ca}^{++}$  in the plasma and a reduction in the excretion of calcium in the urine. Conversely, a negative external balance of inorganic phosphate is accompanied by hypophosphatemia, a tendency for plasma  $\text{Ca}^{++}$  concentration to rise, marked hypercalciuria, and a net negative calcium balance.

Albright, et al,<sup>18</sup> almost 40 years ago, were the first to demonstrate that high phosphate intake could reverse the biochemical picture of primary hyperparathyroidism. Recently, inorganic phosphate has again been used as an important adjunct in the treatment of many hypercalcemic disorders, which are characterized by relative or absolute excesses of bone resorption.<sup>19,20</sup> The administration of inorganic phosphate to these patients with hypercalcemic disorders is associated with a fall in serum calcium, a reduction in urinary calcium, and a positive calcium balance. These effects of inorganic phosphate are probably primarily due to movement of calcium and phosphate ions into the skeleton. Whether phosphate administration to such patients may lead to an increase in the soft tissue content of these ions is as yet an unanswered question. Soft tissue deposition of these ions during phosphate administration may be minimal unless hyper-



phosphatemia is produced in the face of sustained hypercalcemia.

Raisz<sup>21</sup> evaluated the effects of inorganic phosphate on the metabolism of embryonic bone studied in tissue culture; he found that an increase in the concentration of inorganic phosphate in the incubation fluid directly antagonizes the calcium mobilizing effect of parathyroid hormone and enhances the ability of calcitonin to inhibit bone resorption. Finally, a high phosphate diet fed to humans, rats or rabbits for many days can lead to a state of nutritional or physiological hyperparathyroidism with hyperplasia of the parathyroid glands, changes in the skeleton consistent with mild osteitis fibrosa, hypophosphatemia, a high renal clearance of phosphate and low urinary calcium.<sup>13,22-25</sup> A possible explanation for the hypophosphatemia is the creation of a new steady state in which the mildly hyperplastic parathyroid glands require a slightly higher than normal level of plasma  $\text{Ca}^{++}$  to suppress their increased secretory activity. Under these circumstances a higher rate of  $\text{PO}_4^-$  clearance will be maintained and hypophosphatemia will ensue.

Phosphate depletion and hypophosphatemia shift the skeletal dynamic equilibrium with a marked net movement of calcium out of the skeleton; this state is associated with a rapid loss of bone mineral, progressive hypercalciuria, a negative calcium balance, and virtual absence of phosphate from the urine. A bone lesion indistinguishable from rickets and osteomalacia can be seen in humans, rats and dogs after long periods of phosphate depletion.<sup>26,27,28,29</sup> The hypercalciuria of phosphate depletion is due to a decrease in the tubular reabsorption of calcium but the exact mechanism causing the change in the renal handling of calcium is as yet unknown.<sup>30</sup> Phosphate depletion in humans and animals produces a state of physiologic hypoparathyroidism.<sup>27,28,30</sup> In the phosphate depleted state, both in humans and experimental animals, the parathyroid glands are not required for the maintenance of a normal level of serum calcium.<sup>27,28,30</sup> Thus, serum calcium may be normal or even elevated in phosphate depleted parathyroidectomized humans or experimental animals (Chart 3); the administration of small amounts of inorganic phosphate under these circumstances will lead to a rise in serum phosphorus and a marked

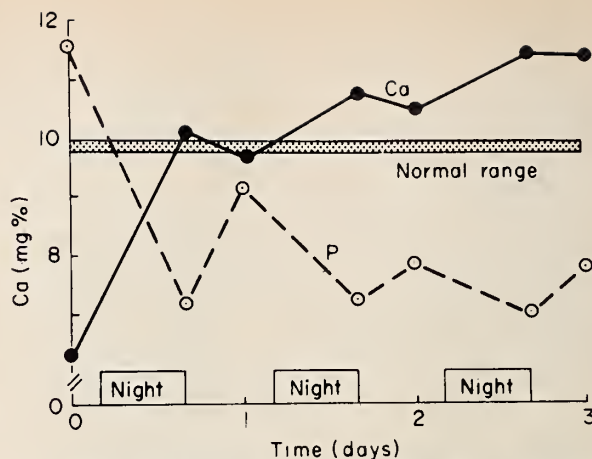


Chart 3.—Effect of low phosphate diet on plasma calcium and phosphorus in a young parathyroidectomized rat. (From Copp, D. H.<sup>28</sup>)

fall in serum calcium.<sup>28,30</sup> In addition, the skeleton of phosphate depleted rats is resistant to the calcium mobilizing effect of parathyroid hormone.<sup>28</sup> It is hard to explain how an animal or human with minimal secretion of parathyroid hormone and the skeleton that is probably resistant to the action of the hormone can maintain a normal or even elevated serum calcium. Baylink et al<sup>29</sup> have shown in the rat that phosphate depletion prevents maturation and mineralization of osteoid while simultaneously causing a three-fold increase in osteoclastic bone resorption. One might expect that the latter could be blocked by calcitonin, but Copp<sup>28</sup> and Kennedy et al<sup>31</sup> have shown that phosphate depletion and hypophosphatemia impair the ability of calcitonin to inhibit bone resorption or lower serum calcium.

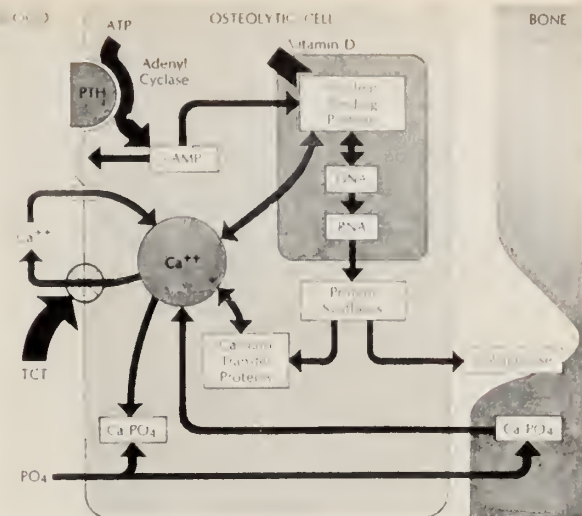
The exact mechanisms by which changes in the body stores of phosphate exert their effects on bone are unknown. It has been suggested that changes in the  $\text{Ca}^{++} \times \text{PO}_4^-$  product of the extracellular fluid, brought about by changes in the level of blood  $\text{PO}_4^-$  favor the movement of these ions into or out of the bone by simple physicochemical equilibrium.<sup>11</sup> However, it is most probable that inorganic phosphate has a direct effect on the intermediary metabolism of all bone cells, possibly by bringing about an alteration in the intracellular calcium. The net effect is inhibition of bone resorption and stimulation of new bone formation.<sup>11-13,21,23</sup> Glimcher<sup>32</sup> suggested that the conversion of inorganic phosphate to organic phospho-proteins in the collagen is essential for its initial mineralization. Also, Raisz<sup>11</sup>

and Nichols<sup>12</sup> have found that the presence of inorganic phosphate in an *in vitro* bone cellular system enhances collagen synthesis, while the removal of inorganic phosphate enhances efflux of calcium and bone resorption.

Phosphate depletion in humans is associated with certain clinical symptoms which have been described by Lotz et al.<sup>27</sup> This syndrome is not frequent and is usually caused by the large intake of phosphate binding antacid, such as aluminum hydroxide gel, used in the treatment of various forms of gastrointestinal diseases.

**Calcium Ion.** Raisz<sup>11</sup> found that a low concentration of calcium ion in the media bathing a tissue culture of fetal rat bone can definitely block the calcium mobilizing effects of both parathyroid hormone and the active metabolite of vitamin D, 25-hydroxycholecalciferol. In thyroparathyroidectomized rats, Nichols<sup>12</sup> has shown that parathyroid hormone increases the uptake of calcium-45 into osteocytes and that the maximal rate of calcium efflux from the skeleton is dependent on the cellular content of calcium. He proposed that the serum calcium directly reflects the calcium content of the osteocyte. Borle noted that physiologic concentrations of parathyroid hormone can increase the intracellular concentration of calcium by augmenting the permeability of the cell membrane and that calcitonin alters the cellular transport of calcium by inhibiting its active efflux from the cells.<sup>15,33</sup> As discussed later, almost all the effects of parathyroid hormone can be attributed to its ability to increase the entry of calcium into the cell; it has, therefore, been postulated that intracellular calcium ion, itself, is the central regulator<sup>10-13,15,32</sup> either by directly affecting cell metabolism through changes in ion activity or by binding to specific nuclear or cytoplasmic proteins that control calcium transport or cell differentiation. This formulation is presented in the theoretical model proposed by Raisz,<sup>31</sup> Chart 4.

**Magnesium Ion.** The exact role of magnesium ion ( $Mg^{++}$ ) in the regulation of bone metabolism and the control of  $Ca^{++}$  concentration in body fluids is unknown. Magnesium is not an integral part of the hydroxyapatite crystal, but a large amount of magnesium is present in the inorganic phase of the skeleton. This is probably located within the crystal lattice and hydration shell of hydroxyapatite. It is probable that the  $Mg^{++}$  content of the bone cells is similar to



**Chart 4.—Theoretical model of an osteolytic cell:** Parathyroid hormone (PTH) is assumed to bind to cell membrane, activating adenyl cyclase to produce a local increased in cyclic AMP (cAMP) concentration. Calcium entry into cell is by passive diffusion along a concentration gradient and is controlled by changes in membrane permeability; cAMP may alter this permeability and could also act on nuclear transcription or other metabolic processes in the cell. Vitamin D may act at nucleus to increase calcium entry or by binding directly to the chromatin to alter nuclear transcription of DNA. It could also synergize with other effects of PTH to increase intracellular  $Ca^{++}$  or stimulate synthesis of proteins involved in resorption (e.g., collagenase) or calcium transport.  $Ca^{++}$  is removed from cell by active transport. The transporting pump may be blocked by calcitonin (TCT), producing a rapid drop in resorption. Phosphate could act by enhancing Ca deposition in bone. Since enzymes cannot work on fully mineralized matrix, this would also prevent matrix removal.<sup>34</sup>

that of the other tissues and that  $Mg^{++}$  is involved in similar pathways of intermediary metabolism.

Changes in the level of  $Mg^{++}$  in the blood and/or in body tissues may affect bone metabolism either by affecting the activity of the parathyroid glands<sup>35,36</sup> or by altering the responses of the skeleton to the action of parathyroid hormone (PTH).<sup>38,39</sup> The most notable effect of  $Mg^{++}$  on bone metabolism in humans is the hypocalcemia of  $Mg^{++}$  deficiency; a similar effect has been reported in dogs, pigs and calves.<sup>37</sup> Such hypocalcemia has been attributed to resistance of the skeleton to the action of PTH.<sup>37,38</sup> The exact cause of the failure of the bone to respond to PTH is unknown. Raisz has shown in tissue culture that PTH-stimulated bone resorption is impaired when the  $Mg^{++}$  concentration in the incubation medium is low.<sup>39</sup> Magnesium



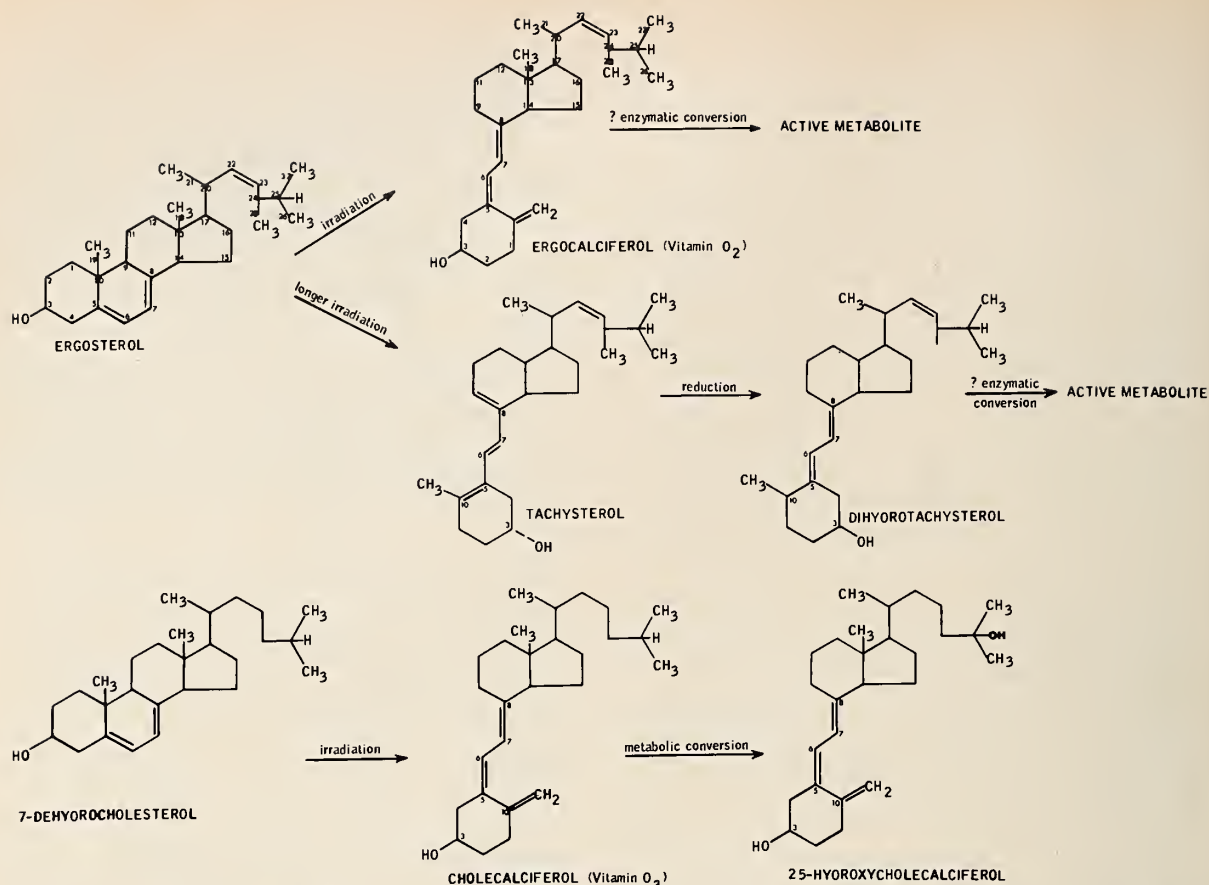


Chart 5.—Schematic illustrating structure, origin and active metabolic products of vitamins D<sub>2</sub> and D<sub>3</sub>. The formation *in vivo* of 25-hydroxycholecalciferol, the active metabolite of vitamin D<sub>3</sub>, has been established. It is likely, but has yet to be proved, that 25-hydroxylation may be a common mechanism of metabolic conversion for the antirachitic compounds *in vivo*; hence, this is shown as probable for dihyrotachysterol and ergocalciferol. Products other than tachysterol are formed after irradiation of ergosterol; hence, tachysterol is usually purified from the irradiation mixture before reduction. Double bonds at carbons 5, 6 and 7, 8 are characteristic of vitamin D compounds that are biologically active. (Data provided through the courtesy of Dr. H. F. DeLuca).<sup>6</sup>

deficient patients do not show the expected increase in cyclic 3'5' AMP excretion after PTH administration.<sup>38</sup> Raisz<sup>11</sup> suggested that PTH unresponsiveness is related to a Mg++ requirement for PTH activated adenylyl cyclase which may represent a fundamental initial step in the cellular action of PTH. It is apparent, therefore, that extracellular and/or intracellular Mg++ concentration must be normal in order to maintain Ca++ and PO<sub>4</sub><sup>=</sup> homeostasis.

**Vitamin D.** Vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol) are produced by the ultraviolet irradiation of ergosterol and 7-dehydrocholesterol, respectively. The former is present in plants and plant products, while the latter is of animal origin. A growing body of evidence<sup>10</sup> indicates that these steroids are hydroxylated at

the 25-position before they can exert a biological effect (Chart 5). This conversion of vitamin D<sub>3</sub> to 25-hydroxycholecalciferol (25-OH-CC) occurs within the liver.<sup>41</sup> The direct addition of 25-OH-CC to transport models of intestine and bone, *in vitro*, produces actions similar to those produced when vitamin D is administered *in vivo*.<sup>42,43</sup> The parent vitamin D, *per se*, lacks such an *in vitro* effect. Evidence for further metabolic conversion of the 25-OH-CC to other metabolites which may be more active in tissues has also been advanced.<sup>44-46</sup>

It has been shown that vitamin D or its metabolites act directly to enhance the gastrointestinal transport of calcium and to augment the resorption of bone; however, there is no unequivocal

evidence for a direct effect of the vitamin on renal handling of divalent ions.<sup>6,47</sup> Although the exact mechanism by which vitamin D acts to enhance intestinal calcium transport remains speculative, there is evidence to indicate that 25-OH-CC enters the intestinal cell to be converted to another metabolite which becomes bound to the nucleus.<sup>45,46</sup> The result is enhanced DNA-dependent RNA synthesis, with consequent stimulation of protein synthesis. In the intestinal cell, two proteins, a specific calcium-binding protein<sup>18</sup> and a calcium-activated ATPase,<sup>10</sup> are produced along the brush border following administration of 25-OH-CC. Although the matter is as yet unresolved, either calcium-binding protein or the calcium-dependent ATPase may be important in enhancing the energy-dependent calcium transport which is stimulated by vitamin D. The increased efficiency of intestinal absorption of calcium in time of need requires the combined action of vitamin D and PTH, although the former seems to be more important. Thus, hypoparathyroid animals receiving a normal intake of vitamin D have defective intestinal absorption of calcium<sup>49,50</sup> and a large dose of vitamin can correct this abnormality. Moreover, vitamin D deficient animals have reduced absorption of calcium despite hypersecretion of PTH.<sup>6,47,49</sup> The action of vitamin D on bone has been less extensively delineated. Twenty-five hydroxycholecalciferol stimulates bone resorption in tissue cultures in a manner quite similar to that produced by parathyroid hormone,<sup>43</sup> and in such a model 25-OH-CC and PTH act synergistically. Both are dependent on the presence of  $\text{Ca}^{++}$  at the plasma membrane or within the bone cell.<sup>11</sup> While there is increasing evidence that PTH exerts its action on bone by activating adenylcyclase, vitamin D has no effect on this system. Raisz<sup>11</sup> suggested that the two agents are "physiologic synergists that act not at the same receptor site in the bone resorbing cells but at separate sites linked so that the effects of one can enhance the response to the other (Chart 4)." He postulated that the synergism between 25-OH-CC and PTH could be explained if PTH controlled  $\text{Ca}^{++}$  entry into the cell and 25-OH-CC controlled  $\text{Ca}^{++}$  entry into the nucleus, with the latter controlling transcription and cellular transformation (Chart 4). In the absence of vitamin D, much larger doses of PTH would

be required to enhance cellular transport of  $\text{Ca}^{++}$  and nuclear transcription.

A vitamin D deficient or resistant state causes classic biochemical and clinical syndromes: rickets in the child and osteomalacia in the adult. They are characterized by: (1) generalized demineralization of skeleton with deformities of weight-bearing bones and pseudofractures, which are symmetrical linear areas of bone resorption at sites where nutrient arteries penetrate the bone, and with histologically defective mineralization of newly formed matrix and relative impairment of the normal bone resorption;<sup>51</sup> (2) hypocalcemia in dogs and rats and either hypocalcemia or normocalcemia in humans, and in all species, the hypocalcemia is relatively unresponsive to PTH; (3) marked impairment of  $\text{Ca}^{++}$  and, secondarily,  $\text{PO}_4^-$  absorption from the gastrointestinal tract; (4) pronounced hypocalciuria; (5) hypophosphatemia, with a high renal clearance of  $\text{PO}_4^-$ ; (6) parathyroid hyperplasia with hypersecretion of PTH.<sup>6,11</sup> These characteristics may all be explained by the basic defects in the bone and gut caused by vitamin D deficiency, *per se*, and the pronounced secondary hyperparathyroidism induced by hypocalcemia.

Conversely, pharmacologic doses of vitamin D cause enhanced bone resorption and increased gastrointestinal absorption of calcium, leading to hypercalciuria and, with greater doses of the vitamin, to frank hypercalcemia. Parfitt<sup>52</sup> has shown that the delay in the return of plasma  $\text{Ca}^{++}$  to normal following the acute hypocalcemic stress of an EDTA infusion, which is characteristic of hypoparathyroid humans (Charts 2 and 6), can be completely corrected by adequate therapeutic doses of vitamin D. Thus, not only can vitamin D replace PTH in the maintenance of a normal plasma  $\text{Ca}^{++}$  concentration under steady-state conditions, it can replace the hormone in producing a normal skeletal response to a hypocalcemic stress.

**Adrenal Steroids.** Mild-to-moderate hypercalcemia has been noted in patients with adrenal insufficiency,<sup>2</sup> and cortisol or its analogues have been used in the treatment of hypercalcemia. Although the chronic administration of these steroids may inhibit the gastrointestinal absorption of calcium and increase its urinary excretion, it is most likely that the ability of these drugs to lower plasma calcium  $\text{Ca}^{++}$  is due to a direct effect upon the skeleton. In hypopara-



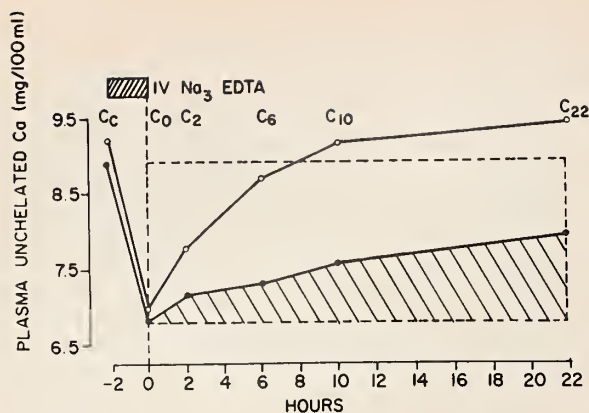


Chart 6.—Response to EDTA infusion. Open circles: mean changes in two normal subjects; closed circles: mean changes in two patients with severe post-surgical hypoparathyroidism. Area under curve of recovery is shaded, area corresponding to instantaneous recovery enclosed by broken line rectangle. (From Parfitt, A. M.<sup>52</sup>)

thyroid dogs (unpublished observations) and rats,<sup>53</sup> adrenalectomy causes a definite increase in plasma  $\text{Ca}^{++}$  concentration, even to hypercalcemic levels. Although Walser<sup>2</sup> suggested that the hypercalcemia of adrenal insufficiency is due to an increase in protein-bound and complexed  $\text{Ca}^{++}$ , we have observed that free  $\text{Ca}^{++}$  concentration rises in adrenalectomized animals (unpublished observations). Furthermore, when pharmacologic doses of glucocorticoids are administered to hypoparathyroid patients, a significant decrease in plasma calcium is seen.<sup>54</sup> Although the exact mechanism whereby steroids exert such an effect on serum calcium is unknown, it may be postulated that glucocorticoids may exert a "tonic suppressive" effect on bone cells responsible for the maintenance of a normal  $\text{Ca}^{++}$  concentration in extracellular fluids. When added to cultures of embryonic rat bone, glucocorticoids can completely inhibit the PTH-induced release of  $\text{Ca}^{15}$  from bone.<sup>55</sup> These steroids are known to be inhibitors of cellular lysosome enzymes. Lysosomes are intracellular membrane-bound vesicles containing potent proteolytic enzymes. During active bone resorption, these enzymes are released from both osteocytes and osteoclasts into the lacunar-canalicular space, and the bone content of these enzymes correlates quantitatively with the magnitude of bone resorption.<sup>56</sup> Glucocorticoids may stabilize lysosome membranes to inhibit release of these proteolytic enzymes,

thereby reducing the magnitude of bone resorption.

**Parathyroid Hormone.** Parathyroid hormone is the single most important regulator of  $\text{Ca}^{++}$  metabolism in mammals. Although the parathyroid glands were first described more than a hundred years ago, their physiologic significance was not appreciated until the early 1900's. The major landmarks in the history of parathyroid hormone are listed in Table 2.

Parathyroid hormone is a single chain polypeptide with a molecular weight of 9,000; its complete structure has not yet been elucidated, but dilute acid cleavage of the purified hormone produces a fragment of about 35 amino acids, which is both biologically and immunologically active.<sup>57</sup> The hormone represents only .004 percent of the wet weight of the parathyroid glands. The currently used assay unit for PTH is the USP unit, and 100 USP units are the amount of hormone which, when injected subcutaneously into a dog weighing 10 to 12 kg, increase the plasma calcium concentration by 1.0 mg per 100 ml within 16 hours. Pure bovine PTH has a potency of 2500 to 3500 USP units per mg, and 1 ml of commercial parathyroid extract (Eli Lilly), contains 100 USP units. The hormone can be measured by bioassay and radioimmunoassay; the rat bioassay can detect 2  $\mu\text{g}$  of the pure hormone while a sensitive radioimmunoassay can measure as little as  $1 \times 10^{-5}$   $\mu\text{g}$ .<sup>6,57</sup> The availability of radioimmunoassay has allowed: (1) quantitation of the dynamic turnover of PTH in the blood; (2) direct investigation of the factors that control PTH secretion; and (3) the development of a newer concept about the pathogenesis of certain disorders.

All actions of PTH tend to promote an increased movement of  $\text{Ca}^{++}$  ion into the extracellular fluid. This is primarily achieved by actions of the hormone to (1) induce bone resorption, (2) enhance renal tubular reabsorption of calcium, and (3) augment intestinal transport of this ion. Another effect of the hormone, that of stimulating urinary phosphate excretion, produces hypophosphatemia and, thereby, secondarily causes plasma  $\text{Ca}^{++}$  to rise.

**P**arathyroid hormone appears to have a dual action on bone. First, it promotes the release of  $\text{Ca}^{++}$  and  $\text{PO}_4^{=}$  from bone mineral into extracellular fluids within minutes, possibly through

TABLE 2.—*Landmarks in the History of Parathyroid Hormone\**

1. 1835—Raynaud described the onset of tetany in dogs following removal of the thyroid gland which involved removal of the parathyroids as well.	of unsuccessful operations, a parathyroid adenoma was removed.
2. 1850—Owen described the parathyroid glands in the rhinoceros.	12. 1930—Beginning in the 1930's, Albright and his colleagues pioneered many of the basic investigations of the clinical picture of deficiency and excess of parathyroid hormone.
3. 1880—Sandström found the glands in several species and correctly identified and located the four glands in man.	13. 1942—Patt and Luckhardt demonstrated the role of the blood calcium in the control of the secretion of PTH.
4. 1895—Kohn showed that the parathyroid developed in the third and fourth branchial arches.	14. 1948—Barnicot and Chang showed that transplantation of the parathyroids into the brains of mice led to direct resorption of the adjacent bone of the skull.
5. 1900—Vassale and Generali were able to produce tetany by parathyroidectomy in cats and dogs even though the thyroid gland was left intact.	15. 1950—Gaillard obtained similar results with combined explants of parathyroids and bone and tissue culture.
6. 1901—Loeb showed that intravenous injections of oxybate, which removed calcium from the blood by precipitation, resulted in tetany.	16. 1956—Talmadge and Elliot used the technique of peritoneal lavage in nephrectomized animals showed the parathyroid hormone had a direct action on bone.
7. 1908—MacCallum and Voegtlin showed that parathyroidectomized animals had a low blood calcium.	17. 1955—Munson showed that pure parathyroid hormone had a direct phosphaturic effect on the kidney.
8. 1911—Greenwald and Gross showed that in experimental parathyroid deficiency, the urinary excretion of phosphorus was greatly diminished and the concentration in blood was greatly increased.	18. 1959—Aurbach and Rasmussen and their associates prepared highly purified preparations of PTH and established that there was only one hormonal product and it had actions on both bone and kidney.
9. 1923-1925—Hanson and Collip each prepared crude, hydrochloric acid, active extracts of the parathyroids which were subsequently used in systematic studies of the physiological effects of the parathyroid hormone in animals and man. This is the commercially available preparation, parathyroid extract, Eli Lilly.	19. 1963—Berson, Yalow, Aurbach and Potts developed the first successful radioimmunoassay of bovine and human PTH.
10. 1891—von Recklinghausen described osteitis fibrosa and distinguished it from other demineralizing diseases of the bone.	20. 1967—Chase and Aurbach demonstrated for the first time that the same enzyme systems (adenylcyclase→cAMP) are affected directly by PTH in bone and kidney and that this represents an important early step in the biochemical mode of action of the hormone.
11. 1926—The first successful identification of hyperparathyroidism with surgical removal of a parathyroid adenoma by Mandl. Another patient, Captain Charles Martell, was studied about the same time in New York and Boston and, after a number	

\*This table is constructed from material in the chapter of Potts and Deftos.<sup>6</sup>

stimulation of osteocytic bone resorption (osteolysis), and, second, it produces extensive bone remodeling under the influence of osteoclastic bone resorption. While the latter process must also liberate  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  ions into the neighboring extracellular fluid, the role of the osteoclastic bone resorption in maintaining plasma  $\text{Ca}^{++}$  under normal conditions is not clearly defined.<sup>10</sup> However, in clinical or experimental situations in which an abnormally high circulating level of PTH is sustained, excessive osteoclastic bone resorption may well contribute to the degree of hypercalcemia. A number of the observed effects of PTH on the skeleton are listed in Table 3, the net result of these effects must be a shift in the equilibrium toward increased bone resorption with the transfer of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  ions into extracellular fluid. These cellular activities must be continuously maintained to counteract the physicochemical

forces which tend to drive  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  ions from extracellular fluid into bone. Therefore, the maintenance of a normal concentration of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  in the extracellular fluid requires a given level of PTH to be present in the circulation at all times. Indeed, recent measurements by radioimmunoassay of the concentrations of PTH in

TABLE 3.—*Effects of PTH on the Skeleton<sup>6</sup>*

1. An increase in the number and resorptive activity of osteoclasts.
2. Increased periosteocytic bone resorption (osteocytic osteolysis).
3. In association with 1 and 2
  - (a) Enhanced lysosomal activity and hydrolytic enzyme formation in osteoclasts and osteocytes
  - (b) Enhanced collagenase activity
  - (c) Enhanced organic acid production by osteoclasts and osteocytes
4. Inhibition of the differentiation and activity of osteoblasts leading to a decrease in the rate of collagen or matrix synthesis.



the plasma have shown that this is the case.<sup>6,58,59</sup>

In the kidney, PTH enhances the tubular reabsorption of calcium and therefore decreases its renal clearance. In their earliest studies, Albright and co-workers<sup>60</sup> noted that an increase in serum calcium produced by the administration of parathyroid extract was associated with a minimal increase in urinary calcium. Three decades later, Talmadge and Krantz<sup>61</sup> observed in rats that parathyroidectomy caused immediate hypercalciuria which persisted until significant hypocalcemia ensued; the administration of parathyroid extract corrected the hypercalciuria. Studies in humans from our laboratory demonstrated that for any given level of serum  $\text{Ca}^{++}$  and filtered load of this ion, the renal clearance of calcium is lower in the presence of PTH and higher when the hormone is absent;<sup>62,63</sup> these studies are most consistent with the conclusion that PTH increases the renal tubular reabsorption of calcium. This action of PTH would explain the frequent finding of a normal or only slightly elevated renal clearance of calcium in patients with primary hyperparathyroidism, the high clearance of this ion in other disorders with comparable degrees of hypercalcemia (malignant tumors with osteolytic metastases, Boeck's sarcoid, and vitamin D intoxication),<sup>62,64</sup> and the hypercalciuria observed in hypoparathyroid patients made normocalcemic with vitamin D or calcium supplementation<sup>63,65</sup> (Chart 7). The relationships between calcium excretion and the level of serum calcium in normal, hypoparathyroid and hyperparathyroid subjects are illustrated in Chart 8; it is evident that low calcium excretion is present in hypoparathyroidism only when the patient is hypocalcemic.<sup>65</sup>

The diffusible fraction of calcium in the blood is filtered at the glomerulus, and 97 to 99 percent of this filtered calcium is actively reabsorbed along the entire length of the nephron. A major portion (65 to 80 percent) of filtered calcium is reabsorbed in the proximal tubule while only 10 percent is transported by the distal convoluted tubule and the collecting duct.<sup>67</sup> Evidence to date strongly suggests that PTH acts on the distal reabsorption of calcium.<sup>68,69</sup> Since the renal handling of calcium is closely related to that of sodium and magnesium, one should always consider the excretory rates of sodium and magnesium in the evaluation of the renal clearance of calcium.

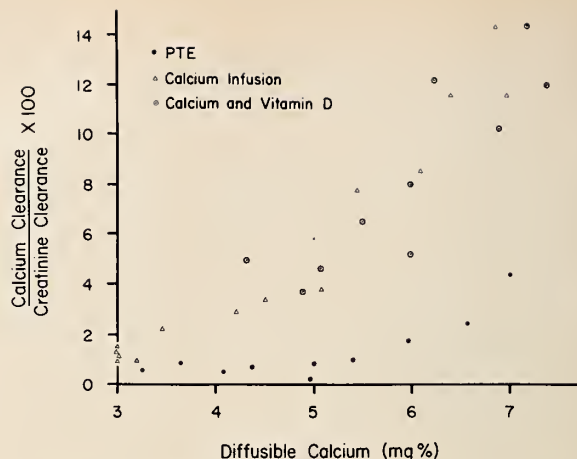


Chart 7.—The effect of calcium infusion, oral calcium and vitamin D, and parathyroid extract on the renal clearance of diffusible calcium at increasing concentrations of plasma diffusible calcium in a patient with hypoparathyroidism. Note that for any given level of plasma calcium the clearance is significantly lower while the patient is receiving parathyroid extract (PTE).<sup>63</sup>

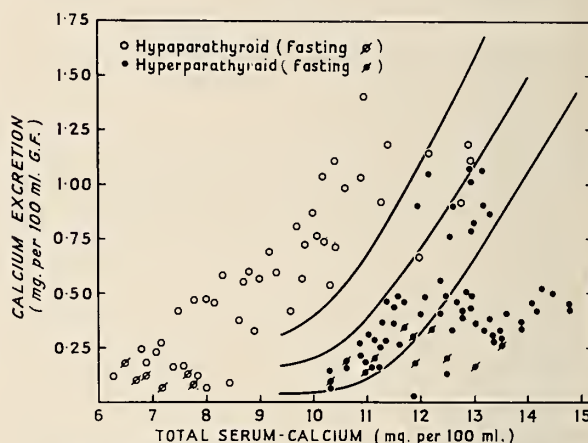


Chart 8.—Serum and urine calcium data in hyperparathyroidism and hypoparathyroidism.<sup>66</sup>

It has also been demonstrated that parathyroid hormone may enhance the renal tubular reabsorption of magnesium in rats,<sup>70</sup> dogs,<sup>71</sup> and man.<sup>72</sup> However, the exact role of PTH in the homeostatic regulation of  $\text{Mg}^{++}$  concentration in the plasma is unclear. During rigid dietary restriction or with excessive gastrointestinal losses of magnesium, the plasma level of this ion falls and the urine becomes free of magnesium. Since hypomagnesemia may stimulate the parathyroid glands,<sup>35,36</sup> increased levels of circulating PTH may be responsible, at least in

part, for the renal retention of magnesium under these circumstances.

In 1911, Greenwald and Gross,<sup>73</sup> demonstrated that the urinary excretion of  $\text{PO}_4^-$  falls and the plasma  $\text{PO}_4^-$  level increases following parathyroidectomy (Table 2). Conversely, augmented renal excretion of  $\text{PO}_4^-$  was one of the earliest effects noted following the administration of parathyroid extract.<sup>74</sup> The renal handling of  $\text{PO}_4^-$  involves filtration at the glomerulus and subsequent active tubular reabsorption: little definitive evidence exists to support the concept of tubular secretion. Under normal conditions, 80 to 90 percent of filtered  $\text{PO}_4^-$  is reabsorbed; thus, the amount of  $\text{PO}_4^-$  cleared is 10 to 20 percent of that filtered at the glomerulus. Parathyroid hormone enhances  $\text{PO}_4^-$  excretion by directly inhibiting tubular reabsorption of this ion. This PTH-induced phosphaturia causes a fall in serum  $\text{PO}_4^-$  level; and this decrease in plasma  $\text{PO}_4^-$  concentration alters the dynamic equilibrium between bone and extracellular fluid in a manner promoting the movement of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  out of bone. An increase in the plasma concentration of  $\text{PO}_4^-$  will antagonize the calcium mobilizing effect of PTH on bone. Thus, the mechanism whereby PTH enhances the renal clearance of  $\text{PO}_4^-$  from extracellular fluid may be of importance in permitting PTH to continuously maintain or slightly increase plasma  $\text{Ca}^{++}$  concentration. In patients with severe renal failure and overt secondary hyperparathyroidism,  $\text{PO}_4^-$  clearance cannot be enhanced further when PTH mobilizes  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  from the skeleton; therefore, both plasma  $\text{PO}_4^-$  and  $\text{Ca}^{++}$  concentrations increase.<sup>75</sup> Under these circumstances the correction of secondary hyperparathyroidism by subtotal parathyroidectomy causes both  $\text{Ca}^{++}$  and  $\text{PO}_4^-$  concentrations to fall (Chart 9).

Many factors other than parathyroid hormone affect the renal handling of  $\text{PO}_4^-$ ; these factors include: (1) dietary intake of phosphate, (2) plasma  $\text{PO}_4^-$  concentration, (3) filtered load of  $\text{PO}_4^-$ , (4) Serum  $\text{Ca}^{++}$  level, (5) the renal handling of sodium, (6) growth hormone, and (7) adrenal glucocorticoids. An increased quantity of  $\text{PO}_4^-$  in the diet can augment clearance of this ion in hypoparathyroid, normal, and hyperparathyroid subjects.<sup>19,20,22,75,77</sup> In the latter group, a high phosphorus intake may result in the renal excretion of 50 to 75 percent of the filtered load

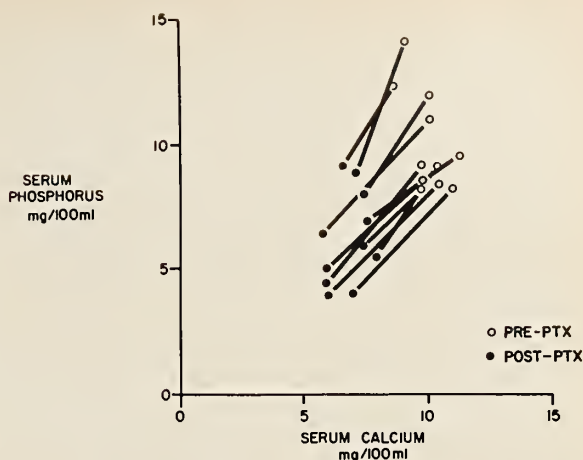


Chart 9.—Changes in total serum calcium and inorganic phosphorus observed in 11 uremic patients before and following subtotal parathyroidectomy (PTX) for severe secondary hyperparathyroidism.<sup>75</sup>

while plasma  $\text{PO}_4^-$  concentration is unchanged or even decreased.<sup>20,75</sup> Conversely, with rigid dietary restriction of  $\text{PO}_4^-$  or the excessive use of phosphate-binding antacids, phosphate clearance falls markedly and  $\text{PO}_4^-$  may actually disappear from the urine.<sup>76,77,78</sup> Although the plasma concentration of  $\text{PO}_4^-$  may certainly affect the fractional reabsorption of this ion, it is possible that the intracellular content of  $\text{PO}_4^-$  in the kidney may also affect the renal handling of  $\text{PO}_4^-$ .

The concentration of  $\text{Ca}^{++}$  in plasma, *per se*, may also influence the renal handling of  $\text{PO}_4^-$ . Eisenberg<sup>79</sup> demonstrated that the hyperphosphatemia and hypophosphaturia of hypocalcemic hypoparathyroid humans could be completely corrected when normocalcemia was achieved by a prolonged calcium infusion. Furthermore, Schussler and his associates<sup>80,81</sup> noted a correlation between hypercalcemia and hypophosphatemia in patients with breast carcinoma and skeletal metastasis; the low plasma  $\text{PO}_4^-$  concentration was attributed to a high renal clearance of  $\text{PO}_4^-$ . They concluded that the hypercalcemia, *per se*, may have been the cause of the phosphaturia and subsequent hypophosphatemia.

Several recent studies have indicated that the reabsorption of  $\text{PO}_4^-$  is closely linked to that of sodium, particularly under conditions of massive saline infusion with expansion of extracellular fluid volume.<sup>82,83</sup> Puschett and coworkers<sup>84</sup> con-



cluded from micropuncture studies that this effect was secondary to the proportional inhibition of the proximal reabsorption of both sodium and phosphate. They found that the infusion of saline solution, parathyroid extract and dibutylcyclic AMP each inhibited the tubular reabsorption of  $\text{PO}_4^{=}$  to a similar extent; and they concluded that PTH-induced phosphaturia is dependent on both cyclic AMP and sodium reabsorption.

In both normal and hypoparathyroid humans and animals, the administration of growth hormone produces renal effects which are opposite to those of parathyroid hormone. For example, the clearance of  $\text{PO}_4^{=}$  falls and that of  $\text{Ca}++$  increases. Furthermore, growth hormone can antagonize the renal effect of PTH.<sup>85</sup> The clinical significance of these observations is unclear. However, it is likely that the high  $\text{PO}_4^{=}$  concentration of plasma and the low  $\text{PO}_4^{=}$  creatinine clearance ratios observed in acromegaly and in pubertal children are due to the increased action of growth hormone. Cortisol and other glucocorticoids are capable of increasing the renal clearance of  $\text{PO}_4^{=}$ <sup>86</sup>; this action may be due to a direct effect of steroids on the renal tubule. It should be emphasized that although  $\text{PO}_4^{=}$  clearance is frequently used clinically to indicate the activity of the parathyroid glands, it is clear from the foregoing discussion that several other factors must be considered before alterations in the rate of  $\text{PO}_4^{=}$  excretion can be completely attributed to changes in the blood levels of PTH.

The effects of PTH to enhance the tubular reabsorption of calcium and to inhibit the reabsorption of  $\text{PO}_4^{=}$  have been shown to be prompt and are closely related to the levels of PTH in the circulation.<sup>62,87,88</sup> In the gastrointestinal tract, the evidence to date, while not conclusive, strongly suggests that PTH enhances the intestinal absorption of calcium.<sup>9,50</sup> This effect cannot be demonstrated within a short period of time but can only be detected hours or days after the administration of PTH.

The mechanisms whereby PTH exerts its effect on the end-organs have received considerable attention, and evidence indicates that the adenylcyclase 3'5'-adenylmonophosphate (cyclic-AMP) system<sup>6,11,49,89,90,91</sup> may be the mediator of the physiologic action of PTH on bone, kidney and gut. Adenylcyclase, an enzyme located on the

plasma membrane, is activated when the hormone is combined with the plasma membrane; the result is accelerated production of cyclic-AMP from ATP. This system may be common to the stimulus-secretion and secretion-action coupling of all endocrine glands. Thus, the acute effect of PTH on bone (Table 3) and kidney are accompanied by the enhanced activity of adenylcyclase and increased intracellular production of cyclic-AMP (Chart 10). In normal persons an increase in the urinary excretion of cyclic-AMP occurs after PTH administration.<sup>92</sup> It is of considerable interest that in one clinical disorder, pseudo-hypoparathyroidism, where the end-organs are refractory to the action of PTH, the administration of the PTH fails to cause the normal rise in the renal excretion of cyclic-AMP (Chart 11).<sup>92</sup>

As yet, there are no definitive data concerning specific metabolic systems which are subsequently stimulated intracellularly by the increased quantities of cyclic-AMP. However, in view of the strong evidence indicating that intracellular concentration of calcium is changed by parathyroid hormone, it may well be that cyclic-AMP in some way regulates the intracellular  $\text{Ca}++$  content. The latter would then be the final transducer between the binding of the hormone to its receptor site and final cellular activity (Chart 4). The adenylcyclase hypothesis of PTH action has permitted certain predictions with respect to the type of drugs and agents which may significantly affect calcium metabolism.<sup>90</sup> Thus, an increase in cyclic-AMP content of the bone should accelerate  $\text{Ca}++$  mobilization and cause an increase in blood  $\text{Ca}++$  concentration, while a decrease should cause a fall in the level of blood  $\text{Ca}++$ . Phosphodiesterase is the intracellular enzyme which is responsible for the breakdown of cyclic-AMP. Imidazole, which activates phosphodiesterase, causes a pronounced and prolonged fall of plasma  $\text{Ca}++$  and  $\text{PO}_4^{=}$  as well as inhibiting the hypercalcemic effect of PTH.<sup>93</sup> Other drugs which inhibit adenylcyclase, such as 2-thiophene, carboxylic acid and 5-methyl carboxylic acid, result in effects opposite to PTH and cause pronounced hypocalcemic and hypophosphatemic responses.<sup>94</sup> If it can be shown that these drugs can correct hypercalcemia without causing serious physiologic dysfunction in other organ systems, they will provide a useful addition to our therapeutic armamentarium.

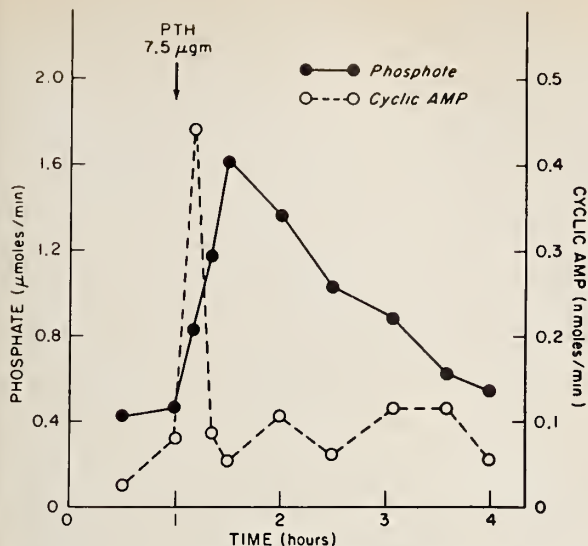


Chart 10.—Chart at top shows effect of an injection of parathyroid hormone (arrow) on the urinary excretion of phosphate and 3',5' cyclic AMP in a parathyroidectomized rat. (From Chase, L. R. and Aurbach, G. D., Proc. Natl. Acad. Sci. (Wash.) 58: 518-525, 1967.)

The lower chart shows effect of parathyroid hormone on adenyl cyclase activity and production of 3',5' cyclic AMP in suspensions of bone cells prepared from rat calvaria *in vitro*. A stimulation by parathyroid hormone is evident within one minute. The insert depicts the maximal stimulation of adenyl cyclase system induced by sodium fluoride. (Courtesy of Drs. L. Chase and G. D. Aurbach).<sup>6</sup>

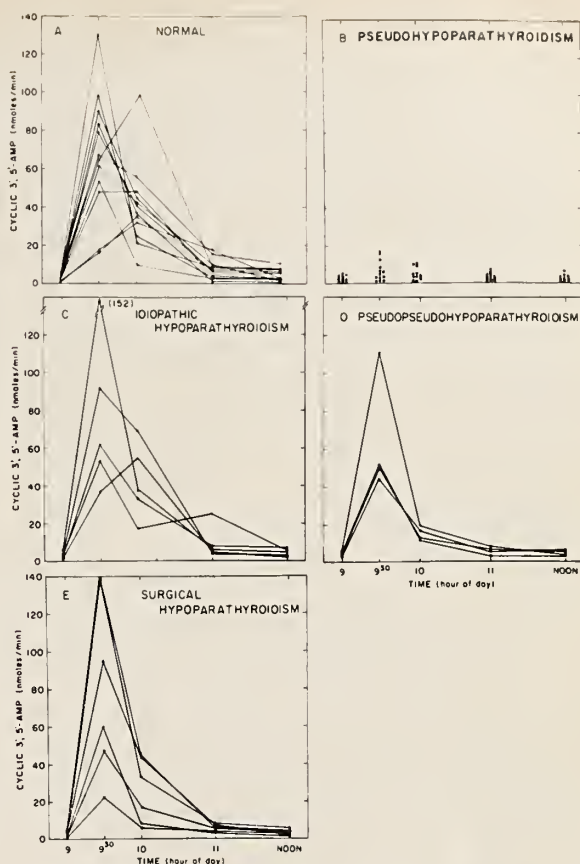
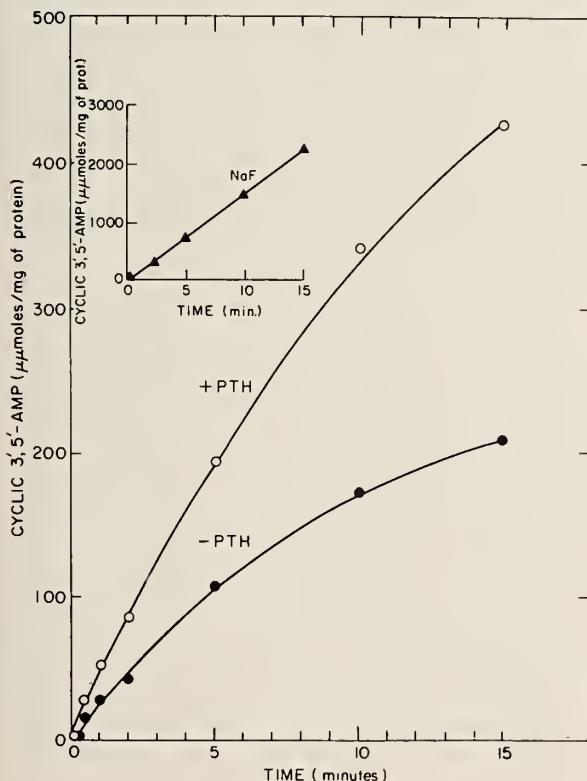


Chart 11.—Effect of parathyroid hormone on the urinary excretion of cyclic 3',5'-AMP. 300 U of parathyroid hormone were infused from 9:00 to 9:15 a.m. and urine collected at intervals of 30 minutes to one hour until noon. Results represent the rate of excretion of cyclic 3',5'-AMP for each interval and are plotted to coincide with the end of the period. Each continuous line represents the pattern of excretion for one subject. Individual patterns of excretion are not shown in B, where each point represents the result for one subject.<sup>92</sup>

Ever since *in vivo* perfusion of the parathyroid glands was performed by Patt and Luckhardt,<sup>95</sup> evidence has progressively accumulated to indicate the fundamental role of  $\text{Ca}^{++}$  in the control of the secretion of PTH. Chart 12 presents the results of a study with an *in vivo* perfusion of the parathyroid glands carried out in our laboratory. Perfusion of the intact parathyroid glands of dogs with hypocalcemic blood (6 to 7 mg per 100 ml) caused an elevation of  $\text{Ca}^{++}$  concentration in peripheral blood in less than an hour and almost immediate rise in renal clearance of  $\text{PO}_4^{--}$ ; perfusion of these glands with hypercalcemic blood (12 to 14 mg per 100 ml) produced a fall in  $\text{Ca}^{++}$  concentration in the



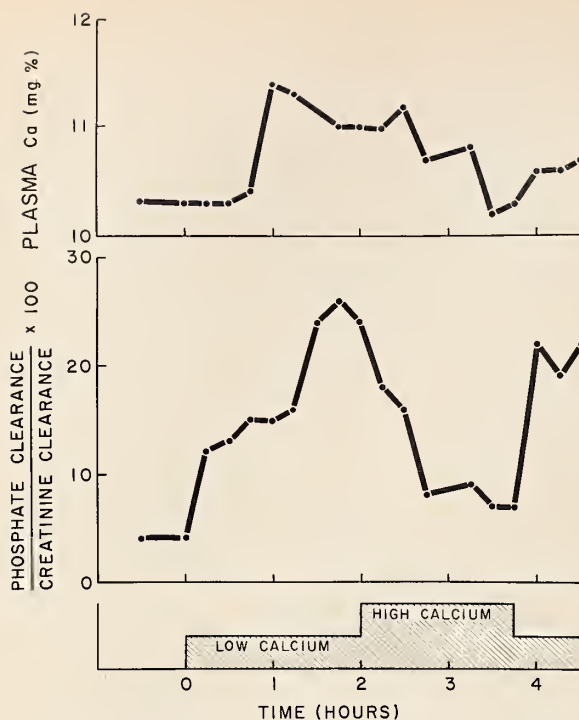


Chart 12.—Response of plasma calcium and phosphate clearance to bilateral thyroparathyroid block perfusion with hypo- and hypercalcemic blood.

systemic blood and a decrease in  $PO_4^{=}$  clearance. Parson and Robinson<sup>96,97</sup> demonstrated that when the isolated tibia of a cat is perfused with blood containing PTH, an increase in the venous  $Ca^{++}$  concentration of blood leaving the tibia occurs within 10 to 15 minutes. These studies illustrate the rapid biologic effect of the hormone on the skeleton.

The development of a sensitive radioimmunoassay for PTH has permitted systematic studies of factors regulating the secretion of PTH in normal and diseased states. Hypercalcemia of 12 mg per 100 ml, produced by the intravenous infusion of calcium salts, causes a fall of plasma PTH to undetectable levels. Conversely, the production of hypocalcemia by the infusion of EDTA causes a 5- to 10-fold rise in the hormone level in the blood.<sup>59</sup> Indeed, available studies indicate that the relationship between the levels of circulating PTH and the concentration of  $Ca^{++}$  in blood is inverse and linear (Chart 13).<sup>6,57,58,59,98</sup>

Evidence also exists indicating that the concentration of  $Mg^{++}$  in plasma is also important in the regulation of PTH secretion. Hypomag-

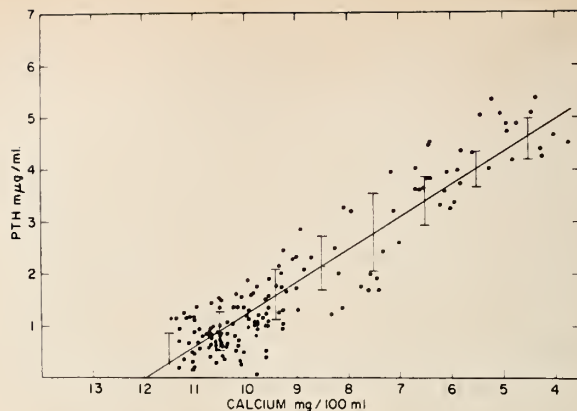


Chart 13.—Relation between concentrations of blood calcium (treated as independent variable) and parathyroid hormone (dependent variable). Linear relation is derived from treating data as a simple regression by the least-squares method. Vertical lines and horizontal bars give standard deviation of observed from predicted hormone concentrations over each interval of the linear function.<sup>6</sup>

nesemia or magnesium depletion may stimulate the parathyroid glands, and hypermagnesemia may inhibit their activity.<sup>35,99,100,101</sup> In a recent study, Massry et al<sup>99</sup> summarized the available data regarding the effect of  $Mg^{++}$  on PTH secretion and demonstrated that an increase in plasma  $Mg^{++}$  concentration of 1.7 to 2.0 mg per 100 ml was adequate to suppress the activity of the parathyroid glands. When these investigators evaluated the simultaneous effects of modest hypocalcemia and hypermagnesemia, they found that a decrease in the level of plasma  $Ca^{++}$  is more potent than an increase in plasma  $Mg^{++}$  concentration in the regulation of parathyroid activity. Sherwood et al<sup>100</sup> evaluated the effect of changes in concentrations of  $Ca^{++}$  and  $Mg^{++}$  on the *in vitro* rate of synthesis and secretion of PTH of bovine parathyroid glands incubated in organ culture. They observed parallel changes in synthesis and secretion of the hormone in response to variation in the concentration of these cations in the incubating media. They concluded that  $Ca^{++}$  and  $Mg^{++}$  are equipotent in blocking hormone release, and that the rate of secretion depends only on the sum of the two ions. Recently, Massry et al<sup>102</sup> presented evidence suggesting that the infusion of strontium chloride to dogs also suppresses the activity of the parathyroid glands. These studies indicate that the activity of these glands may be in-

fluenced by a divalent cation which is not normally present in the body.

The reported levels of circulating PTH from subjects with normal  $\text{Ca}^{++}$  concentration in the blood have varied from one laboratory to another. Buckle et al<sup>103</sup> found levels of 0.1 to 0.2  $\text{m}\mu\text{g}$  per ml<sup>103</sup> while Potts and Deftos reported values of 0.5 to 1.0  $\text{m}\mu\text{g}$  per ml.<sup>6</sup> These values are equivalent to 0.3 to 3.0 USP units per ml. In the steady state, the amount of hormone destroyed or secreted is equal to that secreted, and it is generally agreed that changes in hormone concentration in the blood accurately reflect changes in its secretion rate.<sup>104</sup>

The apparent volume of distribution of the PTH is about 20 percent of body water, and its biologic half-life is about 30 minutes.<sup>104</sup> Using the normal levels of the hormone reported by Potts and Deftos,<sup>6</sup> a 70 kg man will secrete approximately 240  $\text{m}\mu\text{g}$  per min or 0.5 mg per 24 hours under normal conditions; and the amount of the hormone will increase during acute stimulation of the glands to 1750  $\text{m}\mu\text{g}$  per min or 2.5 mg per 24 hours; this is an increase from 1500 to 7500 USP units a day. If one uses the values reported by Buckle et al,<sup>103</sup> the calculated normal secretion rate of the hormone would be equivalent to 300 to 600 USP units a day. That the latter value may be more correct is suggested from our observations that intramuscular injection of 200 USP units 4 to 5 times a day in a normal adult will cause mild hypercalcemia; therefore, 800 to 1000 USP units a day represents a "hyperparathyroid" rate of secretion.

The parathyroid glands do not store large quantities of PTH, and the hormone content of the glands is only .004 percent of their wet weight. The rate of hormone secretion, therefore, depends on the rate of hormone synthesis. As it is most likely that each cell has a maximal capacity to synthesize new hormone, parathyroid hyperplasia may begin when the increased demand for PTH exceeds the secretory or synthetic capacity of the normal number of cells.<sup>105</sup> This is probably the process underlying all forms of secondary hyperplasia—for example, chronic low calcium-high phosphate diet, vitamin D deficient and resistant states, chronic renal failure, and steatorrhea.

Potts and associates called attention to the high degree of parathyroid adaptation which is observed in the chronic hypocalcemic syndrome of cows.<sup>106</sup> An unexplained resistance to the action of PTH develops in the late states of pregnancy, and, when these animals calve and then lactate, severe hypocalcemia develops. For any given decrease in blood  $\text{Ca}^{++}$  level in these animals, the amount of PTH secreted in the adapted state is several fold greater than that occurring in the normal state; however, hypercalcemia of 12 mg per 100 ml completely suppressed the secretion of PTH both in the normal and adapted animals. (Chart 14).

Patients with chronic renal failure provide a clinical situation in which the parathyroid glands are decidedly hyperplastic, and the circulating levels of PTH may be 20-fold more than normal.<sup>6,107,108</sup> In these patients, elevated levels of PTH in blood have been found even when serum calcium was elevated to normal or moderately hypercalcemic levels.<sup>75,108</sup> This apparent non-suppressibility of the parathyroid glands may be explained by the considerable increase in the number of the secreting cells and is probably not due to secretory autonomy of the parathyroid glands.<sup>75,105,107-109</sup> Indeed, the cells of the parathyroid glands of a uremic patient may behave much as they do in normal persons. An elevation of  $\text{Ca}^{++}$  concentration in blood to greater than normal levels might cause a similar degree of suppression of PTH secretion in each cell in both uremic and normal subjects. However, the enormous number of cells in the hyperplastic glands of the uremic patient may provide for the release of large absolute quantities of hormone for any given level of hypercalcemia which is below the concentration necessary to inhibit all hormone secretion from the hyperplastic glands (Chart 15).<sup>75</sup> It is also possible that in some of these patients each cell may produce a greater quantity of hormone under the influence of an equal stimulus. With the same degree of suppression as occurs in normal cells following hypercalcemia, the effect of a large gland mass on total hormone production would be accentuated (Chart 15).<sup>75</sup>

*Calcitonin* (Thyrocalcitonin). A fascinating page in the story of recent research in calcium metabolism has been the discovery of calcitonin. In the ten years which followed the discovery



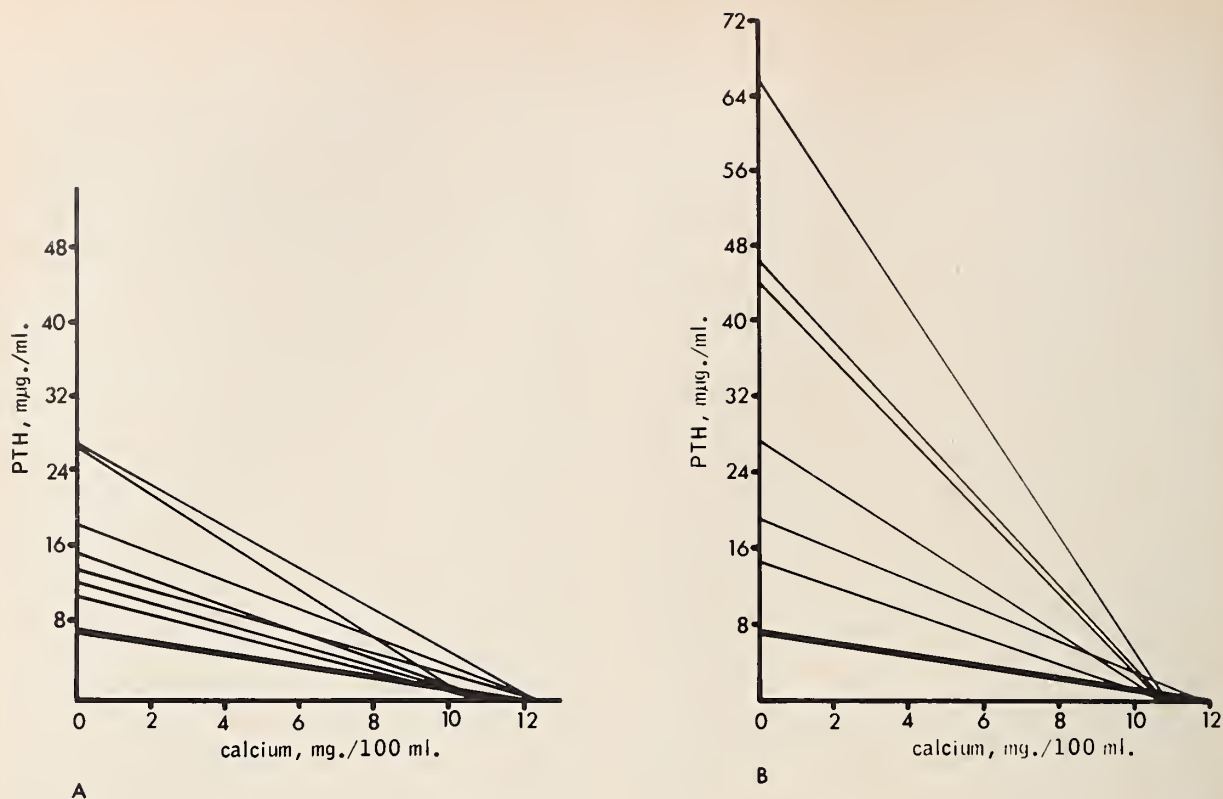


Chart 14.—Comparison of the relationship between blood calcium (independent variable) and blood parathyroid concentration (dependent variable) in a series of parturient cows with secondary hypoparathyroidism. A linear, inversely proportional relationship is evident in animals with secondary hyperparathyroidism as is seen in normal animals (Chart 13). Unlike the findings in normal animals, where pooled data from all animals could be treated simultaneously, it was evident that the response in secondary hyperparathyroidism is unique to each animal. The slope of the line relating hormone secretion as a function of blood calcium is steeper in all animals with secondary hyperparathyroidism than in normal animals (heavy line—data taken from normal animals, Chart 13, and replotted for comparison). The persistence of control by blood calcium of parathyroid hormone secretion, despite excessive rates of hormone production, in animals with parathyroid hyperplasia is evident from the fact that hormone secretion falls to zero in all animals at approximately 12 milligrams per 100 ml in blood calcium. In group B, those with more severe secondary hyperparathyroidism, the slope of the response line is two to eight times as great as the slope of the response line in normal animals.<sup>106</sup>

of this hormonal activity, the identification and isolation, the structural analysis, the synthesis and the characterization of the physiological mode of action of this hormone was achieved.<sup>6</sup> Because the discovery of calcitonin has been so recent, the events leading to and since its discovery will be described in some detail.

Before 1960, it was generally accepted that the precise regulation of plasma  $\text{Ca}^{++}$  concentration was dependent on the negative feedback relationship between blood  $\text{Ca}^{++}$  levels and the rate of secretion of PTH.<sup>110</sup> In 1960, Sander-son and co-workers<sup>5</sup> observed in thyroparathyroidectomized dogs that there was a delay in the correction of hypercalcemia after an intravenous calcium load (Chart 2). The significance of

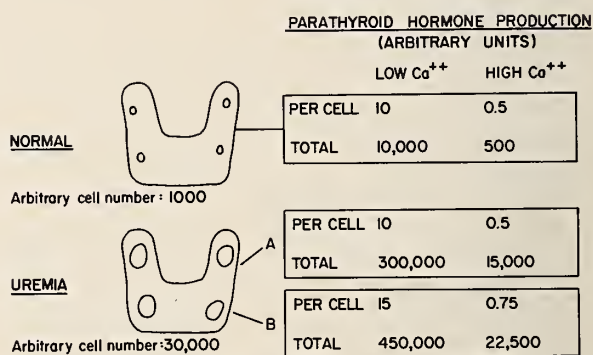


Chart 15.—Theoretical effect of the large mass of the gland in uremia on hormone production. In A, the cell response to calcium level is entirely normal; in B, hormone production per cell is increased but the percentage suppression by elevated  $\text{Ca}^{++}$  is normal. In both instances, total hormone production is high.<sup>73</sup>

these observations was not recognized at the time, but in 1961, Copp and associates<sup>111,112</sup> found that perfusion of the isolated thyroid-parathyroid glands with hyperealemic blood caused more rapid development of systemic hypoealeemia than occurred following thyroparathyroideetomy (Chart 16). They also found that when the perfusate from the thyroparathyroid glands was given to another animal, hypocalcemia developed. From these results, they postulated the existence of a second calcium regulating hormone, which they termed, calcitonin. The thyroid glands and parathyroid glands could not be perfused separately in their experiments in dogs, but two years later the thyroid and parathyroid glands were perfused separately in goats<sup>113</sup> and the results indicated that the thyroid gland rather than the parathyroids was the source of the hypocalcemic substance. In 1963, Hirsch, Gauthier and Munson<sup>114</sup> noted that parathyroidectomy produced by electro-cautery, which injures the underlying thyroid gland as well, resulted in more rapid and marked hypocalcemia than that which was caused by simple, careful surgical parathyroidectomy or even total thyroparathyroidectomy (Chart 17). They suggested that the injured thyroids had released a calcium-lowering substance, which they were subsequently able to prepare from extracts of rat and pig thyroid tissue. These extracts caused both hypocalcemia and hypophosphatemia within an hour after injection into rats,<sup>115</sup> and they termed it *thyrocalcitonin* to indicate the gland of origin. Subsequent studies in rats, dogs, goats, guinea pigs, cows, monkeys and humans have confirmed that the thyroid was the major source of the hypocalcemic principle.<sup>6,116</sup> Utilizing histological and immunofluorescent techniques, Pearce and associates concluded that the production of calcitonin was confined to scattered parafollicular or "C" cells, (Figure 6) which proved to be of ultimo-branchial origin.<sup>117-119</sup> As is summarized in Chart 18, these cells originate phylogenetically along with the parathyroid glands, the thymus, and aortic and carotid bodies from the branchial pouches. In all lower vertebrates other than mammals, these ultimo-branchial glands exist as distinct bodies. The parathyroid glands, which develop later phylogenetically, are present in all air-breathing animals. Their development may be related to the shift away from the marine environment, with its low phosphorus and high cal-

cium levels, to a terrestrial state, where there is exposure to lower calcium and a higher phosphate.<sup>116</sup> Copp and associates<sup>116</sup> were able to find large quantities of calcitonin in the ultimo-branchial glands of chickens, dogs and fish in-

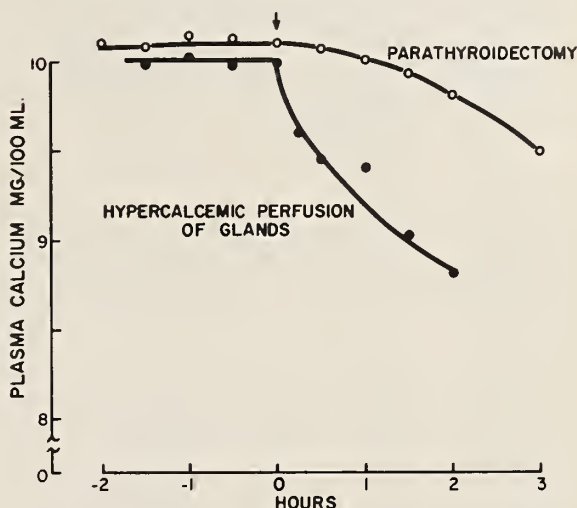


Chart 16.—Comparison of the rate of fall in systemic blood calcium in dogs induced by thyroparathyroidectomy versus regional perfusion of thyroparathyroid tissue with hypercalcemic blood. (From Munson, et al: Recent Progr. Hormone Res., 1963, 24:589-650.)

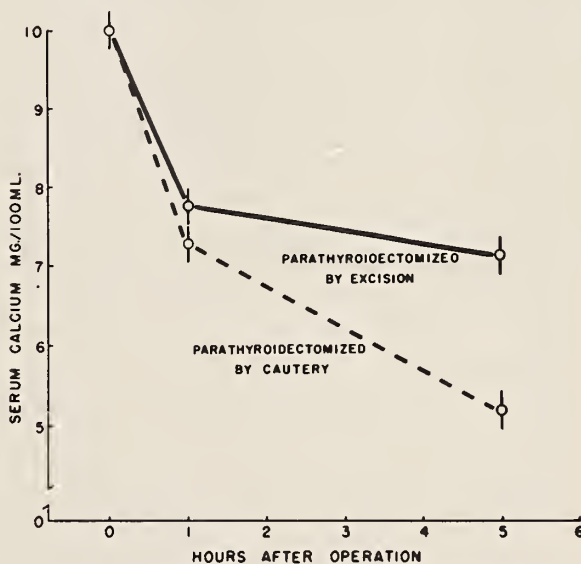


Chart 17.—Comparison of the rate of fall in blood calcium in rats subjected to parathyroidectomy by excision versus parathyroidectomy by cautery. (The latter damages the thyroid and releases calcitonin.) (From Munson, et al: Recent. Progr. Hormone Res., 1963, 24:589-650.)



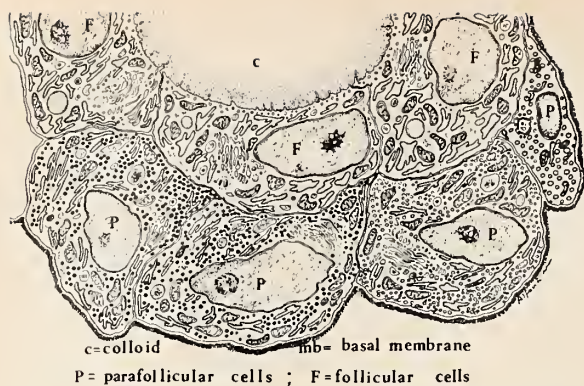


Figure 6.—Schematic representation of the para-follicular cells of the mammalian thyroid gland. (From Azzali, C.: In *Calcitonin*, S. Taylor, Ed. London, Heinemann Medical Publishing Company, 1968, pp. 152-166.)<sup>6</sup>

cluding sharks. Finally, calcitonin has been also clearly demonstrated to be present in the parathyroid glands and thymus of humans.<sup>120</sup> This would explain why total thyroidectomy may not remove all cells capable of producing calcitonin.<sup>121,122</sup>

The complete amino-acid sequences of porcine, bovine, human, and salmon calcitonin have now been determined, and porcine calcitonin has been synthesized.<sup>116,122</sup> It is composed of 32 amino acids with a molecular weight of 3570 to 3590. Although the basic structure of calcitonin is similar in various species, there are a number of differences in individual amino acids in the center of the molecule (Chart 19); the entire molecule seems to be necessary for biological activity. Of some interest, because of its greater biological activity in man, is salmon calcitonin.<sup>116,122,123</sup> Its biological activity is 20 to 200 times greater than that of either porcine or human calcitonin, and it has a longer duration of action (Chart 20).

The biological activity of calcitonin is determined by measuring the decrease in serum calcium level in a young rat given the hormone-containing test sample intravenously. The international bioassay reference standard, provided by the British Medical Research Council, is known as the MRC unit and is equivalent to 5  $\mu\text{g}$  of purified porcine calcitonin. The most sensitive bioassay is capable of detecting as little as 1  $\text{m}\mu\text{g}$  or 0.2 MRC milliunits of calcitonin<sup>124</sup> while a sensitive immunoassay can detect as little as  $1 \times 10^{-5}$   $\mu\text{g}$  or .002 MRC milliunits of calcitonin.<sup>125</sup>

#### Derivatives of Branchial Pouches

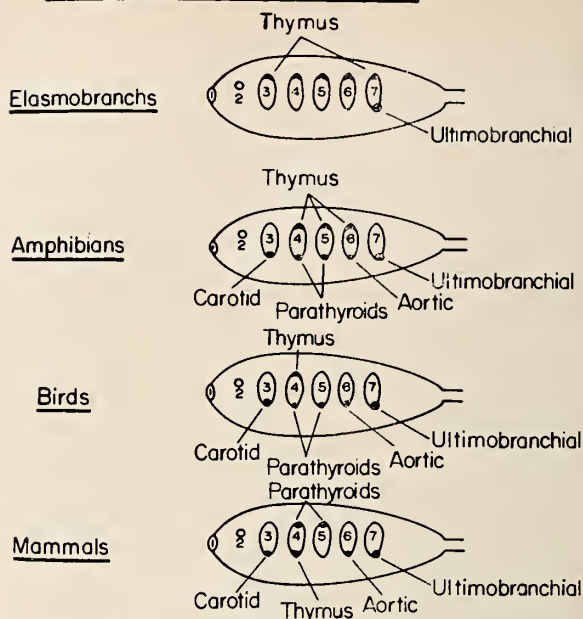


Chart 18.—Embryological development of glandular derivatives of the branchial pouches in various classes of vertebrates. Adapted from Figure 11.26, p 291, in: H. Smith, *Evolution of Chordate Structure*, Holt, Rinehart & Winston, New York, 1960.<sup>116</sup>

The most notable effect of calcitonin is to rapidly reduce the plasma concentrations of  $\text{Ca}^{++}$  and  $\text{PO}_4^-$ . This hypocalcemic action of calcitonin is most profound in young or growing animals and also in other conditions when bone remodeling is active. The effect decreases with age in all species, and the injection of calcitonin has almost no effect on plasma  $\text{Ca}^{++}$  concentration in normal adult subjects. The hypocalcemic action of calcitonin has been shown to occur in animals without parathyroid glands, without the intestinal tract or liver and without the kidneys; hence its action does not depend on the presence of these organs. Furthermore, the action of calcitonin is associated with no change in the soft tissue content of  $\text{Ca}^{++}$  or  $\text{PO}_4^-$ . The overwhelming evidence to date indicates that the most important action of calcitonin is to inhibit bone resorption.<sup>116,122-124</sup> This effect is significantly enhanced by a high  $\text{PO}_4^-$  diet and hyperphosphatemia (Chart 21). Conversely  $\text{PO}_4^-$  depletion and hypophosphatemia may decrease or prevent the hypocalcemic effect of calcitonin.<sup>25,31</sup> This effect of  $\text{PO}_4^-$  may well have been predicted from our earlier discussion of the role of  $\text{PO}_4^-$  on bone accretion and resorption. The action of calcitonin

# PORCINE

H<sub>2</sub>N-CYS-SER-ASN-LEU-SER-THR-CYS-VAL-LEU-SER-ALA-TYR-TRP-ARG-ASN-LEU-ASN-ASN-PHE-HIS-ARG-PHE-SER-GLY-MET-GLY-PHE-GLY-PRO-GLU-THR-PRO-NH<sub>2</sub>

# BOVINE

H<sub>2</sub>N-CYS-SER-ASN-LEU-SER-THR-CYS-VAL-LEU-SER-ALA-TYR-TRP-LYS-ASP-LEU-ASN-ASN-TYR-HIS-ARG-PHE-SER-GLY-MET-GLY-PHE-GLY-PRO-GLU-THR-PRO-NH<sub>2</sub>

# SALMON

H<sub>2</sub>N-CYS-SER-ASN-LEU-SER-THR-CYS-VAL-LEU-GLY-LYS-LEU-SER-GLN-GLU-LEU-HIS-LYS-LEU-GLN-THR-TYR-PRO-ARG-THR-ASN-THR-GLY-SER-GLY-THR-PRO-NH<sub>2</sub>

# HUMAN

H<sub>2</sub>N-CYS-GLY-ASN-LEU-SER-THR-CYS-MET-LEU-GLY-THR-TYR-THR-GLN-ASP-PHE-ASN-LYS-PHE-HIS-THR-PHE-PRO-GLN-THR-ALA-LEU-GLY-VAL-GLY-ALA-PRO-NH<sub>2</sub>

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32

Chart 19.—Comparison of amino acid sequence of porcine, bovine, human and salmon calcitonins. Solid bars indicate sequence positions homologous among all four molecules. Cross-hatched bars indicate the additional positions of homology between salmon and human hormones; stippled bar indicates position where either phenylalanine or tryosine is found in each of the calcitonins. (Amino acid 27 in human calcitonin is isoleucine, and not leucine as shown in this figure.)<sup>123</sup>

## Fall in Plasma Calcium in Rabbits following i.v. Injection of Calcitonin.

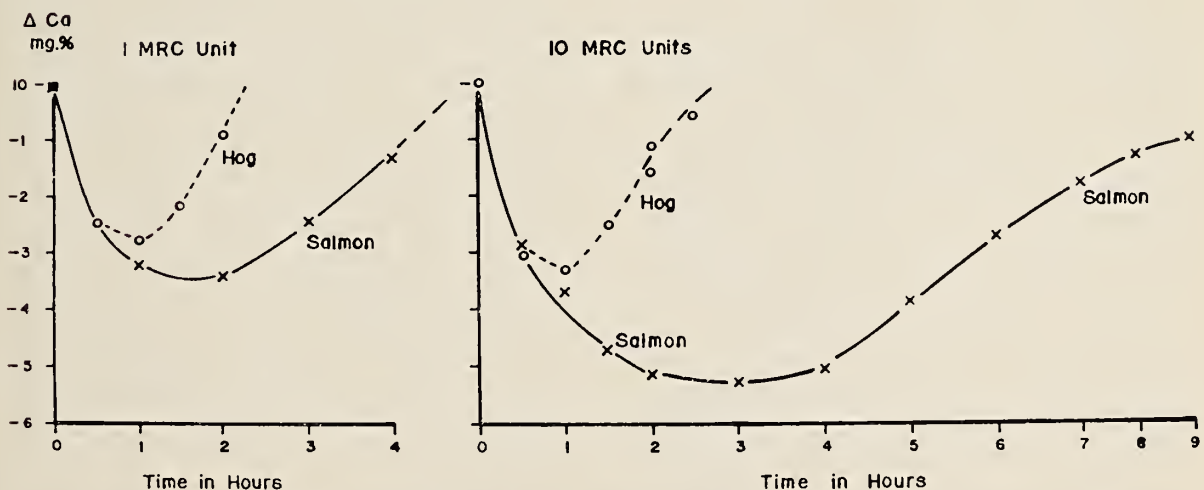


Chart 20.—Comparison of the response in young rabbits to equivalent doses (in MRC units) of salmon and porcine calcitonin.<sup>116</sup>



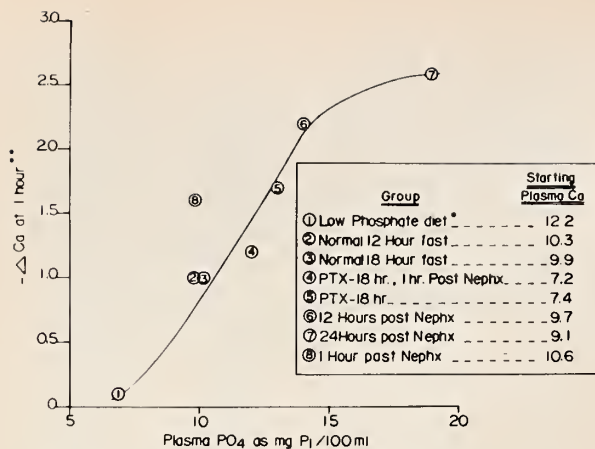


Chart 21.—Relationship of the effect of thyrocalcitonin to the starting plasma phosphate levels. (a) PTX=parathyroidectomized; (b) Nephx=nephrectomized; (c) \*low phosphate diet from Nutritional Biochemical Corporation, Cleveland, Ohio, (d) \*\*plasma changes in mg Ca/100 ml.<sup>31</sup>

on bone is associated with inhibition of both the number and activity of osteoclasts,<sup>126</sup> and, in addition, the osteocytic-osteolysis produced by injection of PTH is inhibited.<sup>128</sup> Thus, the administration of calcitonin acutely reduces the calcium mobilizing effect of PTH in numerous *in vivo* and *in vitro* experiments.<sup>6,116,122,124,127</sup> Following the long-term administration of calcitonin to rats over several weeks, Foster and associates<sup>126</sup> found a decrease in the osteoclast count and a remarkable increase in cortical and trabecular bone. Also, calcitonin was effective in preventing the stunting of growth and osteoporosis which are produced by toxic doses of vitamin A in rats.<sup>129</sup>

The biochemical mechanisms by which calcitonin affects bone resorption remain unknown. Its action does not require vitamin D,<sup>130</sup> and there is strong evidence against its having an effect on either protein synthesis or the adenylcyclase system. Borle and co-workers<sup>33</sup> found that purified porcine calcitonin inhibits the active efflux of Ca<sup>45</sup> from kidney cells in tissue culture, and Raisz<sup>11,34</sup> found a similar effect in tissue culture of resorbing bone cells (Chart 4).

There are important differences between the synthesis, storage, secretion and metabolism of calcitonin in contrast to that of PTH. Unlike the cells of the parathyroid glands, the parafollicular cells appear to be capable of storing large amounts of calcitonin. These stores are sufficient to support secretion for many hours without

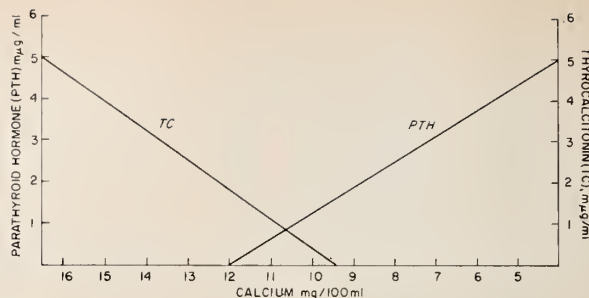


Chart 22.—Effects of changes in serum calcium on the concentration of parathyroid hormone and thyrocalcitonin in peripheral blood. The concentration of thyrocalcitonin is directly proportional to calcium concentration; the concentration of parathyroid hormone is inversely proportional to calcium concentration. (This model is formulated from data obtained from several different species.)<sup>3</sup>

necessitating new hormone synthesis, and to permit several fold increases in secretion rates during a hypercalcemic stimulus.<sup>6,122</sup> Thus, the parafollicular cells are hyperplastic and filled with secretory granules in chronically hypocalcemic, parathyroidectomized rats,<sup>131,132</sup> while the calcitonin content of C cells decreases and remains at reduced levels after prolonged periods of hypercalcemia. In studies utilizing both bioassay and radioimmunoassay,<sup>125,133-136</sup> calcitonin has been detected in the plasma of the rabbit<sup>125,134</sup> and man<sup>133,135,136</sup> when plasma calcium levels are normal. These observations indicate that calcitonin must be continuously secreted in the absence of a hypercalcemic stimulus. Utilizing *in vivo* physiologic studies of Ca<sup>++</sup> released from the skeleton of rat, Klein and Talmage<sup>137</sup> reached similar conclusions that calcitonin is secreted during both normal and mild hypocalcemic states. The level of calcitonin in normal human plasma has been found to range from 150 to 350 milliunits per liter or 0.75 to 1.75 μg per liter.<sup>125,134-136,138</sup> Following a calcium infusion, the blood level of calcitonin may rise as much as five times, depending upon the magnitude of the hypercalcemia.<sup>133-135</sup> It seems clear that the rate of secretion of this hormone is under direct proportional control of the blood Ca<sup>++</sup> concentration (Chart 22) while, as previously noted, PTH is under inverse proportional control. This implies that the regulation of Ca<sup>++</sup> concentration is under dual hormonal control. The continued secretion of both hormones at a normal concentration of blood Ca<sup>++</sup>, the rapid increase in calcitonin secretion with hypercalcemia, and the rapid in-

crease in PTH secretion with hypocalcemia all assure extremely precise modulation of blood  $\text{Ca}^{++}$  concentration through the regulation of bone resorption, which controls the supply of calcium liberated from bone into extracellular fluid.<sup>116,122</sup> It is of interest that the two regression lines for the relationship between plasma  $\text{Ca}^{++}$  concentration and the levels of these two hormones intersect near the normal plasma  $\text{Ca}^{++}$  level<sup>116,122</sup> (Chart 22). Riggs and associates,<sup>139</sup> in studying the plasma kinetics of porcine calcitonin in man with radioimmunoassay, reported a metabolic clearance rate of  $823 \pm 47$  ml per minute. This rate of disappearance is extremely high—3 to 50 times more rapid than that of other polypeptide hormones. If one assumes that the normal mean plasma level of calcitonin is that noted above, this would indicate a turnover or secretion rate of approximately 800  $\mu\text{g}$  or 160 MRC  $\mu\text{U}$  per minute.<sup>139</sup> Further studies regarding the turnover rate of this hormone are necessary to clarify this matter.

Although calcitonin may be of major physiologic importance in preventing hypercalcemia in marine vertebrates, which are exposed to high concentrations of calcium of sea water, and to certain terrestrial vertebrates, such as fowl and herbivores, which ingest high calcium diets, its homeostatic role in dog and man remains unclear.<sup>120,110-142</sup> Although total thyroidectomy in these species does not cause a significant abnormality in the regulation of plasma  $\text{Ca}^{++}$  concentration, this procedure may not remove all calcitonin secreting tissue<sup>120,142</sup>; indeed normal basal blood levels of calcitonin were found in three totally thyroidectomized humans.<sup>112</sup> Sherwood<sup>143</sup> called attention to the fact that endogenous calcitonin is ineffective in controlling the hypercalcemia of hyperparathyroidism. Since all experimental and clinical studies indicate that calcitonin is progressively ineffective with increasing age and since primary hyperparathyroidism usually does not occur before the age of 20 or 25 years, it is conceivable that calcitonin might prevent the manifestations of hypercalcemic-hyperparathyroidism during childhood or adolescence.

(End of Part I. Part II will appear in the next issue of CALIFORNIA MEDICINE.)

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(Continued in Part II, April Issue)



# Specialty Conferences

## Amebiasis — A Symposium

*Discussants:* JERROLD A. TURNER, M.D., WILLIAM P. LEWIS, PH.D.,  
MICHAEL HAYES, M.D., and IRWIN ZIMENT, M.B., M.R.C.P.

*This is the transcription of the regular teaching conferences in infectious diseases held weekly at Harbor General Hospital, Torrance. These transcriptions are edited by Drs. J. A. Turner, I. Ziment and L. B. Guze.*

DR. ZIMENT:\* Amebiasis is sufficiently common in California to warrant all physicians being alert to the possibility of this diagnosis when faced with the presence of compatible symptoms of intestinal or liver disease. The number of cases reported in California each year remains fairly constant: 314 in 1967, 281 in 1968 and 332 in 1969. However, it is fairly certain that many cases are not diagnosed unless an acute complication prompts definitive investigations. At Harbor General Hospital we diagnose about ten cases of amebiasis a year; and we might miss the diagnosis in a number of these were we not practicing eternal vigilance.

Liver abscesses constitute a special problem in that they are often overlooked for a surprisingly long time, and precise diagnosis can be difficult unless modern investigative measures are utilized. The impressive advances that have occurred in the diagnostic realm are not sufficiently appreciated and the participants in this discussion will relate their considerable experience in the employment of these new methods.

Dr. Jerrold Turner will first review the whole clinical spectrum of disease conditions resulting from amebic infection and will discuss therapy.

Following this, Dr. William Lewis will discuss the value of special serologic tests for amebiasis that he has helped develop. These tests have revolutionized the diagnostic approach and will pave the way for future epidemiological studies. Finally, Dr. Michael Hayes will review his experience in the use of liver scanning and its value in the diagnosis of amebic abscess. This new technique, too, has vastly simplified the clinician's task.

### Clinical Review

Dr. Turner:\*\* Amebiasis is generally considered to be a "tropical disease." Such a specific association is unfortunate for it tends to exclude amebic infection from the differential diagnosis of illness acquired in temperate areas. Infection with the protozoan parasite *Entamoeba histolytica* has a world-wide distribution, with the greatest prevalence occurring where inadequate sanitation fosters transmission. Although the disease is more frequently encountered in the developing countries of the tropics, it may occur in any part of the world where protected water sources and waste disposal systems are lacking.

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Amebiasis is readily considered in the differential diagnosis of a patient with a history of exposure in an endemic area, such as the traveler returning from Mexico or a veteran of the Viet Nam conflict. Unfortunately, amebiasis may be overlooked in patients without history of recent foreign travel or in patients whose exposure may have occurred years before the onset of symptoms. Although amebic infections acquired in temperate climates seem to be associated with less overt disease, severe illness frequently arises from amebiasis originating within the United States. We have recently seen patients with advanced amebic colitis and hepatic abscess who have never traveled outside the Los Angeles area.

## Pathogenesis

Ingestion of the cysts of *E. histolytica* in contaminated food or drink leads to colonization of the large bowel by the actively feeding and dividing trophozoites. If the relationship established at this time is a stable one, little or no tissue invasion occurs, and the amebae survive, apparently happily feeding on intestinal bacteria. Under appropriate conditions, the trophozoites will transform into resistant cysts which pass in the feces and become a source of infection for others. This stable relationship is seen in asymptomatic patients. It is well known that a large number of patients in whom amebic liver abscess develops are of this "asymptomatic" category in that they do not have intestinal symptoms. Therefore, it is hazardous to assume that every asymptomatic patient is free of tissue invasion.

The factors which promote invasion of the colonic mucosa are not known, but this intrusion upon host tissue usually occurs at the base of the crypts and extends to undermine the mucosa, producing the classical flask-shaped ulcerations. Amebic trophozoites are seen in the advancing edge of the ulcer with relatively little inflammatory reaction. Inflammation appearing in the area denuded by the protozoal invasion appears to be largely a response to superimposed infection with enteric bacteria. Lesions seen on sigmoidoscopic examination vary from discrete ulcerations associated with normal-appearing intervening mucosa to involvement of the entire mucosal surface with edema and inflammation identical in appearance to that seen in ulcerative

colitis. Pseudopolypoid lesions of amebic colitis may also mimic advanced ulcerative colitis. Colonic ulceration is more frequent in the cecum, proximal ascending colon, sigmoid and rectum, but lesions can occur throughout the colon and may even involve the terminal ileum. An unusual response to amebic invasion of the colon is the formation of abundant granulomatous tissue and edema. This "amebic granuloma" or "ameboma" produces symptoms which may be mistakenly interpreted as representing carcinoma of the colon.

Invasion of the colonic mucosa affords access to venous channels, and amebae then may be carried by the portal vein to the liver. Once in the liver, the amebae may be destroyed by the host's defense mechanisms, or they may initiate abscess formation. The factors which determine the fate of amebae in liver tissue are not known; however, the complication of liver abscess develops in only a small proportion of patients with amebic colitis. Severe amebiasis may develop in any age group and in both sexes, but for unknown reasons occurs with greatest frequency in men between 20 and 50. Asymptomatic intestinal amebiasis refers to patients who have *E. histolytica* demonstrable in stools but who have no symptoms of illness. These individuals are at risk of overt colitis, liver abscess or transmitting the infection to others.

Intestinal amebiasis may be classified as shown in Table 1.

## Symptoms

Amebic colitis encompasses a broad spectrum of disease from mild chronic gastrointestinal complaints to acute, fulminating, hemorrhagic diarrhea. The most clearly defined syndrome, frequently referred to as "acute amebic dysentery," consists of the gradual onset of diarrhea which contains blood and mucus as the disease progresses. The number of stools varies considerably, but is usually about seven to ten in 24 hours. Lower abdominal cramping pain is frequent. Tenesmus occurs with rectal involvement. Many patients are not afflicted with symptoms of anorexia or nausea, but they may avoid eating because it often precipitates a bowel movement. The presence of fever is quite variable but rarely does it exceed 101°F. Examination of the abdomen usually reveals generalized



TABLE 1.—*Classification and Complications of Amebiasis*

<i>Classifications of Intestinal Amebiasis</i>	<i>Complications of Intestinal Amebiasis</i>	
	<i>Intestinal</i>	<i>Extra-intestinal</i>
Asymptomatic	Perforation	Hepatic abscess
Acute amebic colitis	with peritonitis	May rupture or extend into:
"Chronic" amebic colitis—	with localized abscess	pleural cavity
diffuse or localized ulceration	Hemorrhage	lung
	Stricture	peritoneal cavity
	Ameboma	pericardial sac
	Obstruction	abdominal viscus
	Intussusception	Cutaneous amebiasis
	Post-dysenteric colitis	Cerebral abscess

tenderness, most pronounced along the colon. The liver may be slightly enlarged and tender. If untreated, the symptoms of acute amebic colitis may fluctuate in severity for weeks or months, may gradually improve, or may progress to death as a result of massive colon involvement or to the development of one of the complications listed in Table 1.

Symptoms and signs of amebic infections of the colon, other than the acute colitis described above, are quite varied and depend upon the location and degree of the tissue invasion as well as the response of the host to this insult. Localized ulceration may masquerade as appendicitis, diverticulitis or proctitis. The frequent involvement of the cecum with amebic ulceration makes the consideration of amebiasis mandatory in the differential diagnosis of right lower quadrant pain. This should be high on the list in patients with the gradual onset of symptoms or in patients with "chronic appendicitis." Stool examinations and sigmoidoscopy should be performed before a surgical approach. If the diagnosis of amebiasis can be established, operation should be avoided and chemotherapy begun. If the clinical evaluation makes surgical intervention unavoidable, immediate examination of the exudate from the appendix should be performed. If ulcers are seen in the cecum at operation, this is presumptive evidence of amebiasis.

Differentiation of amebic colitis from idiopathic ulcerative colitis, granulomatous colitis or ischemic colonic disease may be impossible on the basis of the clinical picture, sigmoidoscopy and radiographic studies. Amebiasis can be excluded only after careful parasitologic examination. A positive serologic test for amebiasis is

helpful in a patient with negative stool examinations.

Milder forms of intestinal amebiasis have such varied symptoms that no precise categories can be established. Therefore, it is important to consider amebiasis in the evaluation of bowel dysfunction and abdominal pain.

The complications of amebic colitis, other than hepatic abscess, are infrequent, but failure to recognize them may lead to inappropriate or inadequate treatment. It is likely that perforation of the bowel is one of the most frequent and grave complications. Wilmot<sup>1,2</sup> has defined two types of perforation with generalized peritonitis which may occur in intestinal amebiasis. The first type is associated with severe amebic colitis and frequently represents leakage through a grossly intact colon rather than a discrete perforation. This is seen in the patient with advanced colonic disease and is not evidenced by a dramatic onset but may be suspected when abdominal distension becomes persistent and progressive. Ileus and vomiting may be prominent features and dilatation of the colon, resembling the "toxic megacolon" of ulcerative colitis, may occur. Signs of peritonitis such as pain, rigidity and rebound tenderness are not consistently found. If peritonitis of this type develops while the patient is in hospital and is treated conservatively, the prognosis is good for survival although post-dysenteric colitis or stricture may be sequelae.<sup>2</sup> Surgical intervention should be avoided, for total colectomy becomes inevitable if the friable colon is manipulated. Perforation of the second type occurs in those with mild or moderate colitis. The onset is abrupt, with severe abdominal pain and typical signs of peritonitis. Operation, along with spe-

cific anti-amebic therapy, is indicated. Prognosis in this form of the disease is poor.<sup>2</sup>

Localized perforations which become walled-off abscesses or inflammatory masses without associated generalized peritonitis are also seen. The cecal area appears to be particularly susceptible to this complication. Response to chemotherapy or to chemotherapy followed by surgical drainage is usually good.

Amebomas are caused by pronounced cellular proliferative response to the destruction of the normal mucosal barrier. There is no typical pattern on histopathologic examination, but there is proliferation of granulation tissue, fibrosis and abscess formation of varying degrees. This phenomenon may involve a segment of colon and appear as a constricting lesion, or a localized intraluminal mass may develop. Involvement may occur in any portion of the colon, but most amebic granulomas involve the cecum or rectum.<sup>3</sup> The ameboma may be noted not as a part of the clinical manifestations in a patient with acute colitis but incidentally as a palpable mass during examination of the abdomen, or on sigmoidoscopic examination or barium studies of the colon. Amebomas may mimic carcinoma of the colon presenting with obstructive symptoms. Failure to include amebiasis in the differential diagnosis of colonic masses has led to unnecessary resections. Amebiasis has been reported to occur concomitantly with carcinoma, making adequate follow-up of medical treatment of amebomas essential. Lesions within reach of the sigmoidoscope are quickly diagnosed by biopsy and do not pose the problem created by more proximal lesions, in which radiographic disappearance of the mass following treatment is required to exclude carcinoma.

Stricture may occur as a result of severe colitis and is seen most frequently in the rectum. Generally, these strictures resolve without surgical treatment over a period of months following chemotherapy of the amebic infection.

Severe hemorrhage is an unusual complication of amebiasis. A patient was recently taken to surgery at Harbor General Hospital for persistent massive rectal bleeding. A single amebic ulcer eroding a blood vessel was found in the proximal colon. Only patients who do not respond to transfusion and chemotherapy are candidates for surgical treatment, as the entire colon may be involved and surgical repair would

be impossible. Sigmoidoscopic examination is valuable in assessing the extent of involvement and the likelihood of successful anastomosis.

Intussusception may occur. This rare complication is usually cecocolic in location and is precipitated by an ameboma in that area.

One of the less well-known complications of intestinal amebiasis is that of "post-dysenteric colitis" which persists after successful anti-amebic therapy has eliminated the parasites from the lesions and stool. The condition resembles idiopathic ulcerative colitis, and it usually improves over a period of weeks or months of supportive non-specific therapy and does not require further use of antiamebic drugs.

Cutaneous amebiasis, which presents as non-healing, progressive ulcers, may develop by extension of the intestinal infection to the anal and perianal skin or as a complication of surgical procedures that involve an infected colon.

The most frequent complication of intestinal infection is extraintestinal amebiasis which, with rare exception, involves the liver. Although hepatic tenderness and mild liver enlargement frequently develop during acute amebic colitis, the pathologic changes usually are non-specific and amebae are not found in the liver biopsies. Similar symptoms of tender hepatomegaly may develop with the onset of true amebic invasion. Amebic liver abscesses are usually single and located within the right lobe, but multiple abscesses are quite common. It should be strongly emphasized that less than half of patients with amebic liver abscess will have *E. histolytica* found in the stool, and less than half will have a history of diarrhea.

The clinical manifestations of amebic liver abscess will vary with the size, number and location of the lesions. The onset may be gradual or it may be precipitate, with chills and fever. Pain, nearly always present, usually helps localize the abscess; involvement of the overlying diaphragm may produce shoulder pain on the affected side. Aggravation of pain with change of position or with respiration is common. There may be a non-productive cough. Fever occurs in most patients and in a few it is the only symptom. Fever patterns are of wide variety, but usually the fever is low-grade and associated with intermittent profuse sweating. Chills and spiking fevers are also common, sometimes in a regular diurnal pattern. Ano-



rexia, nausea and vomiting may occur. If the disease has been of significant duration, weight loss and weakness may be prominent symptoms.

Physical examination usually reveals enlargement and tenderness of the liver. Frequently, the abscess can be localized by palpation, including careful exploration of the intercostal spaces with light and deep pressure. There may be elevation of the right diaphragm, as detected by percussion and auscultation of the right lung base. Radiographic examination of the chest may reveal elevation of the diaphragm and atelectasis or small effusion at the right base. Abscess of the left lobe of the liver may present with symptoms and signs referable to the epigastrium. Jaundice is distinctly unusual and, if present, may be indicative of a very large abscess.

Laboratory studies are not very helpful. Liver function may have no demonstrable impairment, or there may be mild derangements of no particular pattern. The serum alkaline phosphatase is frequently, but not consistently, elevated. There is usually leukocytosis, with the cell count remaining below 25,000 per cu mm. The hepatocan and serologic test, which are the most helpful, will be discussed subsequently.

Amebic abscesses seldom have secondary bacterial infection, but this question is frequently raised in the initial evaluation of a liver abscess. Distinguishing an amebic abscess from a pyogenic abscess clinically is virtually impossible. There is a tendency for the patient with a bacterial abscess to appear more ill than the average patient with an amebic abscess, and the bacteria may provoke a higher fever and a greater leukocyte response, but the overlap is too great to give these factors much weight. The most direct techniques of differentiation are a trial of specific antiamebic therapy or needle aspiration of the abscess. Patients with amebic liver abscess generally will respond to treatment within 72 hours and will show subjective improvement as well as lessening or disappearance of the fever. Needle aspiration of the abscess affords quick evaluation. Exudate from an uncomplicated amebic abscess has very little odor while the pus from a pyogenic abscess or secondarily infected amebic abscess frequently will have the fetid odor of anaerobic bacteria. Of course, suitable culture media should be inoculated with any material aspirated. The exudate may vary

widely in color and consistency. The exudate of an amebic abscess is not typical pus but results from necrosis of liver parenchyma and admixed blood. These components produce a liquid which ranges from cream color to the classical "chocolate sauce." Greenish or yellowish exudate is not uncommon and should not be interpreted as an indication of secondary infection.

The complications of amebic liver abscess are the results of extension or rupture of the abscess into adjacent organs and spaces or to the exterior through the chest wall or abdomen. The most common site of extension is through the right leaf of the diaphragm to involve the pleura or lung. Actual perforation of the diaphragm is usually preceded by the formation of a mild degree of effusion. Extension may occur into the pleural space or directly into the lung. Occasionally, a broncho-hepatic fistula may develop and the patient then may expectorate contents of the liver abscess. If the abscess penetrates the left leaf of the diaphragm, a similar problem may involve the left lung; but, because of the proximity to the pericardium, it is more likely that rupture will occur into the pericardial sac. This complication may cause pericardial tamponade and death.

Abscesses on the inferior aspect of the liver may either rupture into the peritoneal cavity or into the bowel, biliary tract, renal pelvis or inferior vena cava.

The rare and grave complication of cerebral abscess is nearly always associated with hepatic involvement and represents hematogenous spread.

## Diagnosis

Parasitologists have described several organisms morphologically identical to *E. histolytica* but differing in their biochemical and immunologic characteristics and in their requirements for *in vitro* cultivation. One such variant which often has been referred to as "small race" *E. histolytica* recently has gained wide acceptance as a distinct species, *Entamoeba hartmanni*. Although there is a lack of evidence that *E. hartmanni* produces disease in man, many laboratories do not distinguish it from typical *E. histolytica*. Until the interrelationships of the members of the genus *Entamoeba* are better defined and undisputed markers of pathogenic-

ity are delineated, it is prudent for the clinician to regard any intestinal ameba with the morphologic characteristics of *E. histolytica* as a potential cause of disease.

Demonstration of the organism is still the mainstay of diagnosis. The clinical laboratory should use wet mounts, concentration techniques (for amebic cysts) and, most importantly, permanent stained slides should be prepared from each stool specimen. Gomori's trichrome stain is simple and quite adequate to allow study of nuclear morphology. Several fresh stool specimens should be examined to increase the likelihood of detecting an infection. Purgation is used by some to assure a fresh stool which represents material from the proximal colon. All stool examinations should be completed before the patient undergoes any radiologic studies using barium sulfate. Although examination of aspirate from liver abscess is frequently unrewarding, identification of motile amebae often can be accomplished following incubation of the material with streptokinase and streptodornase.<sup>4</sup>

Sigmoidoscopy provides an excellent opportunity to collect material from lesions or normal appearing mucosa for direct microscopy in saline solution and for fixation in Schaudinn's fluid for permanent staining. Material is best collected from the mucosa with a dull curette or the edge of the biopsy forceps. Transfer of material to the slide is accomplished with an applicator stick. Cotton swabs are not adequate for collection of specimens at sigmoidoscopy. Biopsy at sigmoidoscopy may be helpful. *E. histolytica* appears more prominent in tissue sections stained with PAS or Best's carmine.

## Treatment

There is a large number of drugs available for the treatment of amebiasis, and a variety of regimens employing various combinations have been recommended by different investigators. The difficulty in evaluating the efficacy of drugs in amebiasis is complicated by the differing criteria of cure and the lack of adequate follow-up which mar many of the studies.

The simplified recommendations set forth in the following paragraphs should effectively manage nearly all cases of amebiasis. The drugs employed (dosage is shown in Tables 2 and 3) in these recommended regimens are as follows:

**TABLE 2.—A Schedule for Treatment of Intestinal Amebiasis**

### *Asymptomatic*

1. Diiodohydroxyquinoline (Diodoquin®) 650 mg three times daily for 21 days, and
2. Chloroquine diphosphate (Aralen®) 250 mg four times daily for two days then twice daily for 12 days (for prevention of liver abscess).

### *Amebic colitis*

1. Tetracycline 250 mg every six hours for seven days, and
2. Diiodohydroxyquinoline 650 mg three times daily for 21 days, and
3. Chloroquine diphosphate 250 mg four times daily for two days then twice daily for 12 days; and then,
4. *If symptoms are very severe*, emetine HCl 1 mg per kg of body weight, with maximum 65 mg, intramuscularly daily may be used for 3 to 4 days in addition to the other three agents for amebic colitis listed above.

**TABLE 3.—A Schedule for Treatment of Amebic Liver Abscess**

1. Emetine HCl 1 mg per kg of body weight, with a maximum of 65 mg, intramuscularly daily for 10 days, and
2. Chloroquine diphosphate 250 mg four times daily for two days then twice daily for 28 days, and
3. Diiodohydroxyquinoline 650 mg three times daily for 21 days (to eliminate any intestinal infection).

- Diiodohydroxyquinoline (Diodoquin®) is useful in eradicating the amebae dwelling in the lumen of the bowel. Little of the drug is absorbed from the gut, but it should be avoided in patients sensitive to iodides. It is generally very well tolerated but occasionally causes cutaneous eruptions, nausea and diarrhea. It will increase the blood iodine.

- Tetracycline is extremely useful in the reduction of symptoms in amebic colitis. The side effects are well known.

- Chloroquine diphosphate (Aralen®) has value only for the treatment of extra-intestinal amebiasis. Chloroquine is usually well tolerated, but an occasional patient may have nausea and vomiting. In some patients nervousness, tremulousness and insomnia develop. Incoordination and blurring of vision and toxic psychosis have been reported. The retinal damage reported with prolonged use is not seen at the dosage and duration of therapy recommended for amebiasis.

- Emetine hydrochloride is used for both severe intestinal symptoms and for treatment of



extra-intestinal amebiasis. Side effects consist of pain and tenderness at the injection site, nausea and vomiting, diarrhea, muscular weakness, cardiac toxicity with arrhythmias and fall in blood pressure. Patients should have electrocardiograms during therapy: T-wave changes are common, but the appearance of arrhythmias is a signal for discontinuation of the drug. Patients should be at bed rest during therapy and avoid strenuous exercise for one month following cessation of treatment.

The purpose of the use of multiple drugs for amebic colitis is to alleviate symptoms, eradicate amebae from the bowel and prevent the development of liver abscess. Emetine and tetracycline are effective in bringing about rapid symptomatic response. The three- or four-day course of emetine should be reserved for the very severe cases. In patients with vomiting or ileus, the tetracycline may be administered parenterally. The amebicide diiodohydroxyquinoline is used to eliminate amebae from the bowel, and chloroquine is added to prevent the development of liver abscess.

If a liver abscess is present with colitis, then full doses of chloroquine and emetine should be given as noted below under the treatment of liver abscess.

Both chloroquine and emetine are employed in the treatment of amebic liver abscess to avoid the relapses which may occur if either drug is used alone.<sup>5,6</sup> Diiodohydroxyquinoline is added to eliminate any colonic infection even if stool examinations have been negative.

Needle aspiration has been considered a useful adjunct to chemotherapy in the treatment of amebic liver abscess. Recent evidence indicates that it may offer little benefit in the majority of cases.<sup>7</sup>

Aspiration or surgical drainage may be necessary for very large abscesses or those that may threaten rupture from the inferior surface or left lobe of the liver. Aspiration is useful to determine if bacterial infection exists. Resolution of an abscess may take many months.<sup>7</sup> Persistence of a defect on hepatoscan for periods up to one year and possibly longer in the absence of clinical symptoms does not warrant retreatment.

Two developments have occurred which may soon influence the therapy of amebiasis in the United States. A synthetic compound, dehydroemetine, has been compared with emetine in the

treatment of extra-intestinal amebiasis, and the results indicate that it is as effective as emetine yet has less toxicity.<sup>8</sup> Also, there has been some success in the search for a single drug that would be effective for both intestinal and extra-intestinal amebiasis. Metronidazole (Flagyl®) appears to be very promising in this respect, and following continued evaluation may replace the combined drug therapy of amebiasis.<sup>9</sup>

Chemoprophylaxis is possible with either hydroxyquinolines or arsenicals. The use of these compounds for the prevention of amebiasis requires daily doses and is recommended only under highly unusual circumstances.

## Serology

Dr. Lewis.\* Well-known difficulties in demonstrating the presence of *E. histolytica* in the stool by classical parasitologic means have encouraged a series of workers to explore serologic methods of detecting amebic infections. The first extensive studies were done by Craig<sup>10</sup> using a complement fixation method that differed somewhat from the methods used today. Beginning in 1956, Dr. J. F. Kessel and I began a study of serologic tests for toxoplasmosis, and we gained considerable feeling for the capabilities of Boyden's indirect hemagglutination test.<sup>11</sup> The method seemed to be well suited to amebic serology as it was able to detect very low levels of antibody with acceptable specificity. *E. histolytica* was the best source of antigen for human serodiagnostic studies. Later, ameba cultures grown with a stable "L" form of symbiont were found to be specific and acceptable. Antigen is now prepared from the HK-9 strain of *E. histolytica* growing in symbiont-free (axenic) culture by the method developed by Diamond.<sup>12,13</sup>

Largely through the efforts of Doctors Kessel, Turner and Molina-Pasquel, a battery of serum samples was assembled, and the results of tests were published by Kessel, et al.<sup>14</sup> Since that time we have tested many more serum samples and can say that the data, discussion and conclusions in that paper were sound and representative. Patterned after our work, the indirect hemagglutination test for amebiasis is being performed by the Parasitic Diseases Unit, National Communicable Disease Center, Atlanta, Georgia.

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TABLE 4.—Antibody Reactivity by Hemagglutination (HA) and Complement Fixation (CF) Tests in Amebiasis Groups and Uninfected Controls

Reactivity*	Extra-intestinal		Intestinal				Uninfected			
	1. Liver abscess		2. Dysentery and/or lesions		3. Enteric symptoms mild		4. Asymptomatic		Controls	
	HA	CF	HA	CF	HA	CF	HA	CF	HA	CF
Negative	0	0	2	9	5	56	48	73	98	101
Low	0	0	6	12	32	16	27	10	2	0
Medium	3	5	10	32	67	11	36	13	1	0
High	32	15	115	39	43	1	29	5	0	0
Totals										
Number positive of number examined	35/35	20/20	131/133	83/92	142/147	28/84	92/140	28/101	3/101	0/101
Percent positive	100	100	98	90	97	33	66	28	3	0

\*Hemagglutination test: negative, < 8; low, 8-32; medium, 64-512; high, > 512. Complement fixation test: negative, < 8; low, 8-16; medium, 32-128; high > 128; anticomplementary sera not included.  
From Kessel, et al.<sup>24</sup>

In Table 4 the serologic results are presented in relation to clinical groupings that tend to separate patients showing extensive, invasive amebiasis from other persons who harbored *E. histolytica* in the stool without current symptoms. The groupings were:

1. *Liver abscess* with parasitologic demonstration of amebae in the pus or walls of the abscess.

2. *Dysentery* present, with blood and mucus in the stools, or demonstrable amebic lesions on proctoscopic or sigmoidoscopic examination. Trophozoites of *E. histolytica* were found.

3. *Enteric symptoms, mild*, was a catch-all epithet for a group of patients who had symptoms ranging from vague abdominal discomfort to watery diarrhea without blood and mucus. No lesions were seen when proctoscopic examinations were performed although *E. histolytica* was found in the stools.

4. *Asymptomatic infections*, in which there were no reported signs or symptoms of clinical amebiasis. Cysts were predominant in the stools.

5. *Uninfected controls* were students with no past history or symptoms or current indication of amebic infection.

Results showed that when tissue invasion was proven and extensive, as with amebic liver abscess or classical amebic dysentery, the indirect hemagglutination (IHA) and complement fixation (CF) tests were almost always positive, and titers were usually high. At the other extreme,

serum samples from uninfected controls were essentially non-reactive. It soon became apparent that the IHA test was more reactive than the CF test, producing higher titers that tended to remain for years after persons were successfully treated for amebiasis. It is useful as a sensitive screening test for amebic antibodies. The CF test measures a different but overlapping set of antibodies. It is less reactive than the IHA test, and a positive test indicates a relatively recent amebic infection with probable activity of the amebic lesions within the last year or two. In both tests, the height of the antibody titers gives additional information about the extent and timing of the infections. It is evident that results of the two tests are supplementary, and it is best to test diagnostic serum specimens by both methods.

Our studies with the gel-diffusion precipitin test show that it is quite comparable to the CF test, and the number of precipitin bands correlates rather well with the CF titer of the same serum. Comparisons with other workers have shown that the indirect fluorescent antibody test gives results that are more comparable to the IHA titers.

Some of the major conclusions of our work are as follows:

- Different strains of *E. histolytica* resemble each other antigenically, but they are not identical. No distinct groups or serotypes comparable to those of poliomyelitis have been found, and the DKB and HK-9 strains of *E. histolytica* are ac-



ceptable for detecting antibody from all geographic locations that have been studied.

- Classical morphologic methods for demonstrating the presence of amebae still provide the most definitive information for making a diagnosis of amebiasis, and serologic studies should be supplemental rather than a main-line method. Serology is indirect, at best, and it is most useful to the clinician in helping establish the cause of a space-occupying lesion of the liver in which it is difficult and impractical to demonstrate the amebae. The serologic response is strongest and most predictable in these cases. Serologic tests can be used but are seldom needed to help diagnose classical amebic dysentery, as the amebae are usually present in large numbers and are easy to demonstrate. Serologic tests are least useful in diagnosing vague gastrointestinal ailments, as the antibody titers are lowest and least predictable in this group, and it is difficult to determine whether they are associated with past or recent infection.

- The timing for appearance of antibodies is variable and uncertain, as the date of primary infection is seldom known. Antibodies in high titer have been found in the earliest stages of symptomatic amebic liver abscess, but they may be delayed for a month or two in intestinal amebiasis, especially if lesions are small in size or number.

- Antibody titers are slow to change even after therapy, and paired or serial serum samples drawn at two- to six-month intervals are appropriate if titer changes are being investigated.

- As antibody persists for a long time after treatment, many people (perhaps 50 percent) in highly endemic and unsanitary environments have antibody from past infections without signs or symptoms of current illness with titers that may be at any level. This is not the case among American travelers, but particular care is necessary in evaluating the significance of antibody in foreign nationals, and the complement fixation titer is particularly useful.

## The Liver Scan in Hepatic Amebiasis

Dr. Hayes: I would like to demonstrate the value of the liver scan by means of several short case histories to illustrate how the scans aid in

diagnosis, treatment planning and follow-up of the patient with amebic abscess.

Two basic types of agents are available for liver scanning: those which are excreted by the parenchymal cells, such as iodine 131 and rose bengal, and those which are taken up by the reticuloendothelial system. Agents of the latter type are generally more suitable for static imaging of the liver because of their relatively slow clearance. Their mechanism of localization is nonspecific; almost any intravenously administered small particulate matter will be taken up by the reticuloendothelial system and, if labeled with a suitable radioisotope, will be a satisfactory scanning agent. The most commonly employed agents of this type are gold 198 colloid and technetium 99m sulfide colloid. Microaggregates of albumin in the 1 to 5 micron size range, labeled with technetium 99m, are the agent used at this institution. Our usual dose is 1 to 2 millicuries intravenously 10 to 15 minutes before scanning. As the technetium labeled agents give only 1 rad or less radiation dose to the liver,<sup>15</sup> there need be no concern about repeating the examination at timely intervals. Although short-lived agents such as those labeled with technetium 99m or indium 113m are preferable because of lower patient radiation dose and improved scan statistics, their diagnostic accuracy has not yet been clearly demonstrated to be higher than that of the older and still widely used agent, gold 198 colloid.<sup>16</sup>

Scans are performed on a 3-inch crystal rectilinear scanner, a 10-probe scanner or a scintillation camera with a divergent collimator. In our department there is no clear preference for one type of scanner over another for liver imaging. All three seem equally adequate to the task of diagnosing lesions.

Multiple views have been clearly shown to enhance diagnostic accuracy,<sup>17</sup> and hence anterior, right lateral and posterior scans are done on most patients receiving liver scans. Since liver scanning is based on uptake of radioactive material by normally functioning tissue, pathologically involved areas show up as non-radioactive areas or "holes."

Scanning has been shown to have a high diagnostic accuracy in detecting amebic abscess.<sup>18</sup> This accuracy is due more to the nature of the pathologic process than to our ability to detect

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small liver lesions, for in amebic disease the abscess is usually fairly large by the time it is suspected. As a point of reference, lesions of 2.5 cm or less in diameter are rarely detected in clinical scanning.<sup>15</sup>

It should be stressed that a liver scan defect of itself is a non-specific finding, and differentiating between the diseases which cause discrete space-occupying defects, such as metastatic disease and bacterial or amebic abscesses, is the province of the clinician.

## Reports of Cases

**Case 1.** A 52-year-old man was seen ten days after right colectomy for a cecal lesion. He had fever, elevation of the right diaphragm and a leukocyte count of 7,700 per eu mm. Liver scan on 2 June 1969 (Figure 1, A and B) showed a well-defined defect in the right lateral scans. The anterior view showed a probable second lesion within the left lobe. By 10 July 1969 both lesions and liver had decreased in size in response to antiamebic therapy.

**Case 2.** A 31-year-old man was referred with hepatic enlargement and tenderness and a leukocyte count of 19,000 per eu mm. He had been in Mexico three months previously. On 11 April 1969 right lateral (Figure 2 A) and anterior liver scan (Figure 2 B) showed two large defects. By 24 April 1969 both defects and liver size had decreased in response to therapy. Scans

on 13 May 1969 showed residual defects despite further clinical improvement.

**Case 3.** A 33-year-old man presented with a confusing array of signs, symptoms and findings. Although scans (Figure 3) aided in diagnosing amebic liver abscess, this case underlined the need for multiple views. On 6 February 1968 a definite residual defect was seen on the posterior view but not on the anterior view.

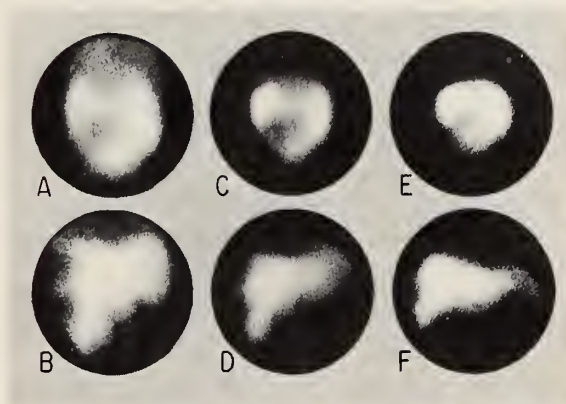


Figure 2 (Case 2).—Right lateral (A) and anterior (B) on 11 April 1969; right lateral (C) and anterior (D) on 24 April 1969; right lateral (E) and anterior (F) on 13 May 1969. Serial scans showing decrease of liver size and resolution of abscesses in response to antiamebic therapy.

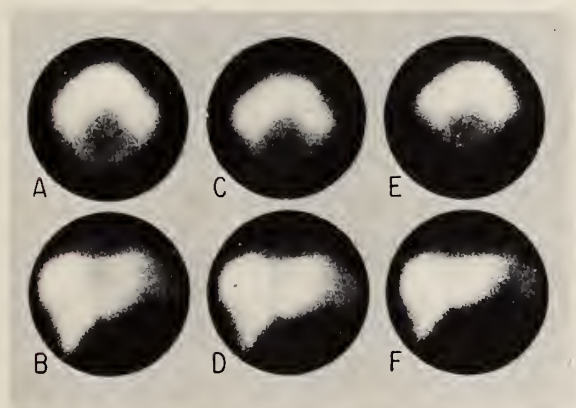


Figure 1 (Case 1).—Right lateral (A) and anterior (B) liver scans on 2 June 1969. Right lateral (C) and anterior (D) liver scan on 11 June 1969. Right lateral (E) and anterior (F) liver scans on 10 July 1969. Scan series shows response of abscess and liver size to antiamebic therapy. Scans on 11 June 1969 illustrate that a lesion may be missed if multiple views are not obtained.

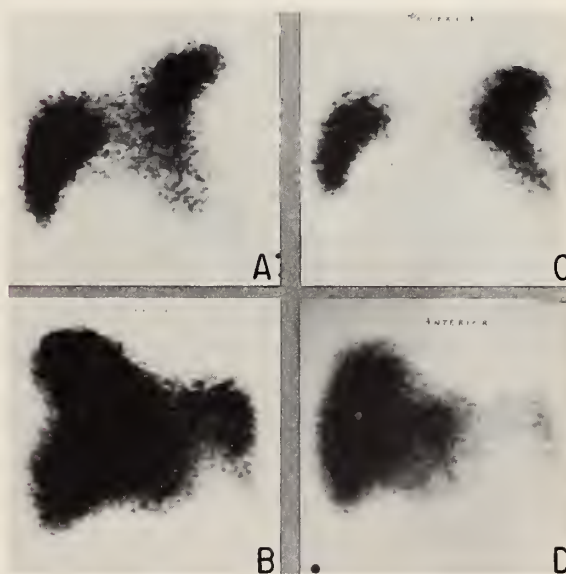


Figure 3 (Case 3).—Posterior (A) and anterior (B) on 16 January 1968. Posterior (C) and anterior (D) on 6 February 1968. Scans illustrating the necessity of multiple views. Posterior view on 6 February 1968 shows a clearcut residual defect not visualized on the anterior view on the same date.



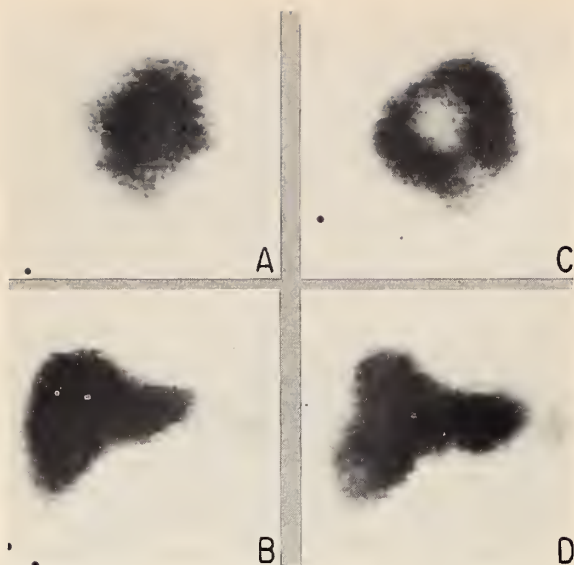


Figure 4 (Case 4).—Developing abscesses in a 47-year-old woman which were missed on right lateral (A) and anterior (B) of 5 April 1968, but clearly visualized on 10 April 1968 (C, D).

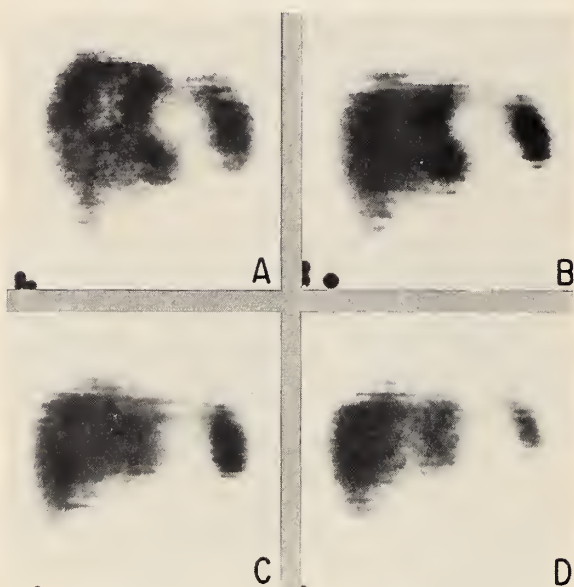


Figure 5 (Case 5).—Serial anterior liver scans on 8 November 1968 (A), 5 December 1968 (B), 13 January 1969 (C), and 7 April 1969 (D) showing value of scanning in monitoring response of liver abscesses to antiamebic therapy.

*Case 4.* A 47-year-old woman presented with diarrhea associated with fever, chills and right flank pain of a week's duration. Before coming to this institution she had received a course of antibiotic therapy from a private physician. Initial liver scans (Figure 4, A and B) on 5 April

1968 were interpreted as normal by our division. Repeat scans on 10 April 1968 (Figure 4, C and D) revealed not one but two communicating defects in the right lobe.

*Case 5.* A 24-year-old man presented with a history of anorexia and weight loss over a period of three months. On admission fevers as high as 106°F were noted, and the liver was tender. The initial scans on 8 November 1968 (Figure 5 A) showed at least two space-occupying defects highly suggestive of liver abscesses. Follow-up scans (Figure 5, B and C) showed decrease in size of the liver and lesions with antiamebic therapy. On 7 April 1969 (Figure 5 D) the scan was interpreted as possibly showing a recurrent lesion in the hilar region.

We have seen that liver scanning is quite helpful in delineating the site, size and number of abscesses.<sup>19,20</sup> The appearance alone of the scan, if supported by a typical history and physical examination, can almost clinch the diagnosis. The scan is certainly helpful in planning a diagnostic needle aspiration. The specific scanning agent or imaging machine employed is not nearly as important as the physician's decision to scan. The referring physician should request a liver scan at the first suspicion of amebic disease, he should insist on multiple views of the liver and he should get repeat scans at timely intervals.

Scan findings are usually clear-cut: the liver is enlarged and a large abscess or abscesses are easily visualized. Occasionally a developing abscess may be missed at first, but a repeat scan in a few days will probably reveal the lesion, as these abscesses grow quite rapidly. Serial follow-up scans during specific antiamebic treatment show a dramatic response; both the size of the liver and the size of abscesses decrease promptly. Complete resolution of scan defects may, however, take several months.<sup>7</sup>

In conclusion, the liver scan is a safe, atraumatic, reproducible procedure which aids in diagnosis, treatment planning and follow-up of amebic liver disease.

## Concluding Remarks

Dr. Ziment: Early diagnosis of amebiasis is dependent upon the physician's traditional index of suspicion being maintained at a high level. The disease may present as a primary intestinal disorder ranging from mild distress to severe

dysentery with various possible colonic complications developing in the chronic state.<sup>21</sup> Conventional studies of the colon may lead to an early diagnosis, and knowledgeable sigmoidoscopy may be more valuable than other investigations. Careful examinations of the stool or of specimens obtained at sigmoidoscopy are essential, and the help of a competent parasitologist or technician can be invaluable.

Extra-intestinal amebiasis rarely involves sites other than the liver, and a single hepatic abscess is the usual finding. Clinical examination may be surprisingly unhelpful even when the liver abscess is very large, and all clues such as an unusual right pleural effusion must be given careful consideration. The advent of liver-scanning techniques has greatly enhanced the clinician's ability to diagnose a liver abscess, and the development of serological tests has rendered the differential diagnosis a simple matter in cases where the serology is strongly positive for amebiasis. Serological tests are not generally available, and at present the indirect hemagglutination test and complement-fixation test are obtainable only at one place in California, namely Torrance Memorial Hospital, 1425 Engracia Avenue, Torrance, California 90501. It is of interest that the Microbiology Laboratory at Torrance Memorial is receiving about 60 to 80 blood specimens a week, of which up to one-third are serologically positive for amebiasis. Many of these positive cases are from the Fresno area.<sup>22</sup>

The participants in this review have detailed the various procedures required to establish the diagnosis of amebiasis, and the various recommended treatment regimens have been outlined.

It is hoped that this information will enable physicians to diagnose and manage cases of amebiasis with greater ease and confidence.

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## WATCH OUT WHEN LOOKING FOR GONORRHEA IN A NEWBORN

"The discharge in gonorrheal ophthalmia in newborns is characteristically profuse and may be under considerable pressure behind the lids. Purulent material may therefore spurt from the eye when the lids are forcibly separated. For this reason the physician should protect his own eyes when examining these patients."

—DAVID S. FRIENDLY, M.D., Washington, D.C.  
Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Edema Formation and the Use of Diuretics

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SLEISINGER:\* There are a number of pathological disorders characterized by generalized retention of fluid and a need for removing this fluid from the body. In this regard, of course, the diuretic agents are in the forefront of therapeutic considerations. Dr. Earley will discuss the indications and the use of diuretic agents.

DR. EARLEY:† I would like to begin with a discussion of factors which appear to be involved in the regulation of sodium excretion and how these mechanisms may operate abnormally in the presence of a disease characterized by sodium retention and the formation of edema or ascites. I will then discuss the role diuretic agents may play in the reversal or amelioration of the pathogenesis of sodium retention and point out some of the important complications of diuretic therapy.

Chart 1 is a schematic summary of the major factors apparently involved in the normal regulation of sodium excretion. An increased dietary

intake of sodium is followed by thirst and a release of antidiuretic hormone which leads to retention of the ingested water. In this manner the increment in dietary sodium is accompanied by the retention of an isotonically equivalent volume of water which expands the extracellular fluid (ECF) volume. This expansion of ECF initiates an increased renal excretion of sodium which will continue until the increment in dietary sodium is eliminated.<sup>1</sup>

Several factors seem to be involved in linking the expansion of ECF to increased excretion of sodium. One of these could be increased glomerular filtration rate (GFR) which would provide a larger amount of sodium and water for tubular reabsorption. If such an increased filtered load of sodium exceeds the existing reabsorptive capacity of the tubules, the surfeit will spill over into the urine.

Another factor effecting an increased excretion of sodium is a decrease in the secretion of aldosterone. Suppression of aldosterone secretion known to result from an increased intake of so-

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dium, would decrease the rate of tubular sodium reabsorption and permit more of the filtered sodium to escape into the urine. There is an increasing amount of evidence that intrarenal hemodynamic changes are involved in the regulation of tubular sodium reabsorption. These changes include an effect of decreased renal vascular resistance or increased renal perfusion pressure to lower the rate of tubular sodium reabsorption, possibly as a consequence of increased peritubular capillary hydrostatic pressure and a lowered rate of capillary absorption.

Finally, there is some evidence that there may be a hormone which is released in response to expansion of ECF volume and suppresses tubular sodium reabsorption. The renal tubular effects of such a hormone would be opposite to those of aldosterone.

Thus, as illustrated in Chart 1, there may be at least four categories of factors involved in the regulation of sodium excretion in response to changes in ECF volume.<sup>2</sup> It is likely that under normal conditions none of these pathways alone dictates the regulation of the sodium balance. Experiments have been designed in which filtration rate is controlled at a depressed level, yet the kidney still increases sodium excretion in response to increased ECF volume.<sup>3</sup> When changes in aldosterone activity are avoided, either by adrenalectomy and replacement of hormone, or by providing excessive amounts of the hormone, the kidney still will eventually achieve sodium balance.<sup>3,4,5</sup> A similar lack of pre-eminence is probably true for the other specific factors influencing sodium excretion, and these multiple mechanisms undoubtedly work in concert, overriding each other when necessary to maintain volume integrity of the extracellular compartment. Just as neither mechanism alone determines the normal regulation of sodium excretion, it is likely that neither one alone accounts for sodium retention and edema formation in disease states.

Chart 2 is a schematic representation of abnormalities in fluid distribution and sodium excretion that may occur in congestive heart failure. I would like to emphasize that there are two somewhat independent mechanisms at play, one behind the heart and one in front of the heart. More than three decades ago Harrison<sup>6</sup> championed the concept of backward heart failure, which proposed that in right heart failure a ma-

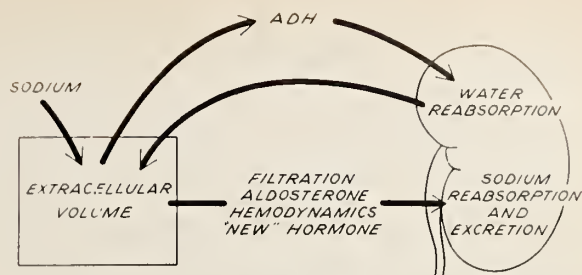


Chart 1.—Factors involved in the interrelationship between extracellular fluid volume and sodium excretion.

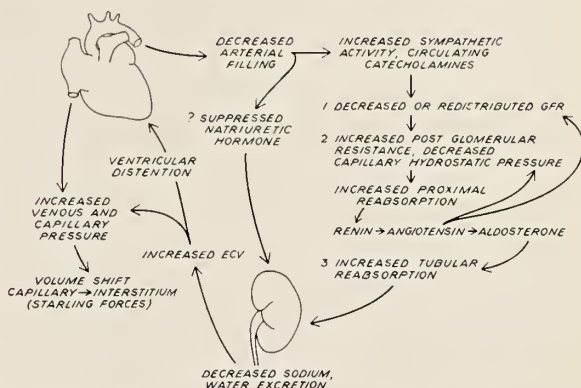


Chart 2.— Possible sequence of events associated with increased sodium reabsorption and edema formation in low-output cardiac failure.

jor factor leading to sodium retention was increased venous pressure resulting from the inability of the heart to handle the venous return. The increased venous and capillary pressure should lead to a redistribution of extracellular fluid from the vascular compartment into the interstitial spaces. It was proposed further that increased renal venous pressure somehow resulted in sodium retention by the kidney. A short time later Warren and Stead<sup>7</sup> emphasized the concept of forward heart failure, which proposed that inadequacy of the arterial circulation leads to sodium retention and edema formation as a result of some unspecified effect on renal hemodynamics.

In view of what appears to be "the light" of current knowledge, it seems reasonable to incorporate the fundamental features of both "backward" and "forward" heart failure into a modernized scheme for sodium retention and edema formation.<sup>2</sup> Failure of the heart as a pump results in increased venous and capillary hydrostatic pressure, with the highest pressures in the most dependent portions of the body. The in-



creased capillary hydrostatic pressure will cause a redistribution of volume from the vascular compartment to the interstitium as a result of redirection of the Starling forces operating across capillary walls. A similar redistribution of extracellular fluid may be an important feature of edema formation in other diseases, although there need not be an increase in capillary hydrostatic pressure. In the nephrotic syndrome, hypoalbuminemia results in a pronounced decrease in plasma colloid osmotic pressure, and this would produce a shift of volume between capillary and interstitium which is qualitatively similar to that resulting from increased capillary hydrostatic pressure. In liver disease with ascites, there is increased portal venous and capillary pressures and usually decreased plasma albumin resulting from underproduction by the diseased liver. This combination of altered Starling forces results in localized extravascular accumulation of fluid in the form of ascites.<sup>8</sup> Thus, the formation of edema or ascites may begin as a purely local phenomenon due to changes in the capillary beds specifically affected by the underlying disease.

Returning to the example of heart failure shown in Chart 2, one notes there is another, somewhat unrelated, influence of the diseased heart on sodium balance. When the heart fails as a pump, there is an inadequate circulatory output, sometimes described as "decreased arterial filling" or "decreased effective ECF."<sup>9</sup> An inadequate cardiac output results in several changes that could affect sodium excretion. Activity of the sympathetic nervous system is increased, and very likely so are circulating catecholamines. Such increased sympathetic activity, either through direct renal innervation or as a result of circulating catechols, may account for the increased renal vascular resistance usually present in heart failure.<sup>10</sup> Retention of sodium would be favored by the resultant decreased GFR or possibly by a redistribution of filtrate to nephron populations of maximal reabsorptive capacity.<sup>11</sup> In addition, increased renal vascular resistance should decrease hydrostatic pressure in the peritubular capillary circulation, a change that may enhance proximal tubular sodium reabsorption.<sup>2</sup> Increased proximal tubular reabsorption diminishes delivery of sodium to more distal parts of the nephron, and this decreased delivery may trigger the juxtaglomerular apparatus to increase the output of renin.<sup>12</sup> Increased plasma renin will lead to increased for-

mation of angiotensin from plasma alpha-2 globulin; and angiotensin has two recognized actions, both of which could decrease sodium excretion.

The vasoconstricting effect of angiotensin may decrease GFR and augment tubular sodium reabsorption as a consequence of decreased peritubular capillary hydrostatic pressure.<sup>2</sup> In addition, angiotensin stimulates the secretion of aldosterone,<sup>13</sup> and the latter hormone has a direct effect to increase tubular sodium reabsorption. In this scheme the forces promoting the accumulation of extravascular fluid are located behind the heart in the venous and capillary circulation, and the forces promoting renal sodium retention are localized in front of the heart in the arterial circulation.

The kidney may be regarded as responding in an appropriate manner to what it perceives as an inadequate arterial circulation. In this sense the retention of sodium may be looked upon as an effort of the kidney to replenish the ECF and to compensate for the failure of the heart to provide an adequate circulation. However, the failing heart is not inclined to accept the expanded ECF so generously provided by the kidney, since it already may be pumping the venous return at maximum capacity. This compensatory expansion of ECF volume will further increase venous and capillary pressures so that much of the retained fluid would be translocated into the interstitium in the form of more edema or ascites or both. To the extent that the retention of sodium and water expands the vascular volume and produces ventricular distention, there may be further decompensation of the heart as cardiac output falls along the descending limb of Starling's curve.

Where, if anywhere, do diuretics enter therapeutically into this scheme of heart failure? By forcing the excretion of sodium and decreasing extracellular fluid volume, venous and capillary pressures may decrease, this decrease resulting in the movement of edema fluid from the interstitium into the vascular compartment. Perhaps more important, cardiac output may increase to the extent that ventricular distension is diminished by forced diuresis. Thus, a desirable therapeutic result of diuretics may be achieved by reversal of some of the pathogenetic mechanisms in heart failure. However, this gratifying sequence of events may not always occur; and in some instances forced diuresis may not increase cardiac

output,<sup>14</sup> but instead may worsen the circulatory status.

As mentioned above, edema formation in the nephrotic syndrome relates primarily to diminished plasma albumin. Decreased plasma protein osmotic pressure initiates the formation of edema by translocating fluid from the vascular to interstitial compartment, and vascular volume generally is decreased in the nephrotic syndrome. Therefore, the stimuli initiating sodium retention are analogous to those produced by bleeding the normal individual. In a patient with hypoalbuminemia, "bleeding" into the interstitial spaces should activate the sequence of events leading to sodium retention as shown for heart failure in Chart 2.

In the case of cirrhosis of the liver, or other liver diseases characterized by the accumulation of ascites, the sequence of events leading to sodium retention is more difficult to formulate. It seems well established that cardiac function (output) may not be compromised in patients with liver disease and ascites.<sup>15,16</sup> It would seem possible, if there were not evidence to the contrary, that the formation of ascites (related to local forces in the portal circulation) could deplete the circulating volume and initiate sodium retention. However, in cirrhosis of the liver, cardiac output is usually normal or increased and the intravascular volume may be expanded.<sup>16</sup> In many patients with cirrhosis and ascites, blood pressure is often low in spite of increased cardiac output, indicating pronounced peripheral vasodilatation, but renal vascular resistance is often quite high.<sup>16,17</sup> It is possible that a generalized decrease in peripheral vascular resistance may lead secondarily to neural or neurohumoral renal vasoconstriction, and the latter change may account, at least in part, for sodium retention.

With this survey of the pathogenesis of edema as a background, I would like to turn now to a discussion of diuretic agents. Chart 3 illustrates the sites along the renal tubule where sodium reabsorption occurs through functionally different mechanisms and where the major classes of diuretic agents appear to exert their effects.<sup>18,19,20</sup> In the proximal tubule approximately 70 percent of the filtered sodium is reabsorbed isotonically. Another 20 percent is reabsorbed in the medullary portion of the ascending limb of Henle's loop; 5 to 10 percent is reabsorbed in the more distal cortical part of the loop of Henle; and finally some-

## TUBULAR SITES OF SODIUM & WATER REABSORPTION

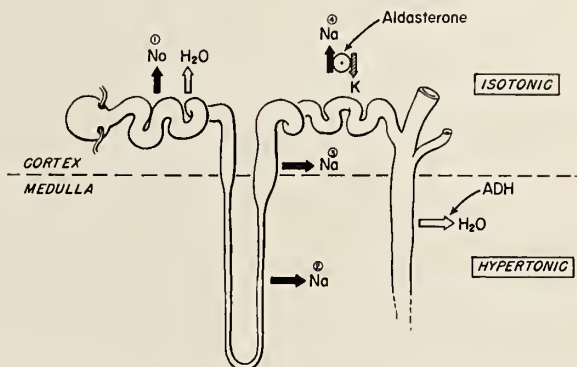


Chart 3.—Renal tubular sites of sodium reabsorption action of diuretic agents.

thing less than 5 percent of the filtered sodium is reabsorbed in the distal nephron under the stimulation of aldosterone. At this aldosterone-sensitive distal tubular site there is a reciprocal relationship between sodium reabsorption and potassium secretion. From a quantitative point of view, if a diuretic agent extensively interfered with sodium reabsorption in the proximal tubule it could affect the excretion of up to 70 percent of the filtrate. In terms of normal glomerular filtration rate, this would be the excretion of approximately 100 liters of urine a day.

Fortunately, the pharmaceutical industry has not yet developed a diuretic agent that will extensively block sodium reabsorption throughout the proximal tubule, for such a drug would be a very hazardous one. Interference with reabsorption in the early part of the ascending limb of Henle should result in excretion of 20 to 30 percent of the filtered sodium, and it is this site of tubular reabsorption at which ethacrynic acid appears to exert its effects. Ethacrynic acid thus may result in the excretion of 20 to 25 percent of the filtered sodium when administered in optimal doses. If this excessive blockade of tubular reabsorption were sustained for long periods, severe complications could occur. Five percent of the filtered sodium appears to be reabsorbed at a slightly more distal site in the cortical portion of the ascending limb, and it is at this site that thiazide diuretics interfere with sodium reabsorption. Furosemide appears to block reabsorption throughout the length of the ascending limb and possibly to a lesser extent in the proximal tubule,



overlapping the sites of action of ethacrynic acid and thiazides. Ethacrynic acid and thiazides have additive effects to promote the excretion of sodium,<sup>21</sup> and because of these separate tubular sites of action there is a physiological basis for combining the two agents therapeutically. Ethacrynic acid and furosemide would not be an intelligent combination of diuretic agents since both exert their major effects at the same tubular site.<sup>22</sup>

Agents that block the distal tubular mechanism, where aldosterone stimulates sodium reabsorption and leads to potassium secretion, promote the excretion of only 1 to 2 percent of the filtered sodium. Therefore, the aldosterone antagonist, spironolactone, is a relatively weak diuretic agent when administered alone.<sup>19</sup> The same should be true for triamterine, which interferes with sodium reabsorption at the same tubular site. However, triamterine is not an aldosterone antagonist, and it will decrease sodium reabsorption independent of aldosterone activity. In contrast, the natriuretic effect of spironolactone occurs only in the presence of aldosterone-stimulated sodium reabsorption.<sup>23</sup> Spironolactone and triamterine are most effective when used in combination with another diuretic agent that blocks sodium reabsorption at one of the more proximal tubular sites. For example, combining a thiazide with spironolactone or triamterine can result in a complementary effect of the two agents to promote the excretion of sodium, possibly at rates in excess of that achieved with either of the two drugs alone.<sup>19</sup> Such an additive effect should occur also when ethacrynic acid is administered in combination with an aldosterone antagonist or triamterine.

The relative power of various diuretic agents is shown in Table 1.<sup>19</sup> Here organomercurials have been assigned a power of 1 and are used as a standard for comparing the natriuretic power of other agents. Under optimal experimental conditions, organomercurial diuretics will block the reabsorption of approximately 20 percent of the filtered sodium. By comparison furosemide is almost twice as powerful; ethacrynic acid is about one and a half times as powerful; thiazides are approximately one-fourth as powerful; and spironolactone and triamterine may be at best only approximately one-tenth as powerful as organomercurials.

When administered in optimal dosage, the numerous thiazide derivatives are equal in terms

**TABLE 1.—Relative Power of Commonly Used Diuretics**

Organomercurials .....	1*
Furosemide .....	2
Ethacrynic Acid .....	1.5
Thiazides .....	0.25
Triamterene .....	0.10
Spironolactone .....	0.10

\*Under optimal experimental conditions organomercurial diuretics may result in the excretion of about 20 percent of the filtered load of sodium. The power of the other diuretic agents, determined under similar conditions, is expressed relative to that of organomercurials.

of their ability to interfere with sodium reabsorption.<sup>19</sup> Any alleged difference in power among the thiazide diuretics refers to the size of the dose required to achieve a maximal effect. However, even when 2 grams a day is necessary to achieve a maximal natriuretic effect, as is the case with chlorothiazide, the patient can easily tolerate this small amount of medication. Also, all of the thiazide derivatives increase urinary potassium excretion to approximately the same extent.<sup>18,19</sup> The major difference among the various thiazides is found in the duration of action. Chlorothiazide is cleared by the kidney at a very rapid rate, and its duration of action is limited to two to four hours,<sup>18</sup> requiring a schedule of administration every four to six hours. Hydrochlorothiazide has an intermediate duration of action; and, at the opposite extreme, chlorthalidone has a duration of action of 48 to 72 hours.<sup>18</sup> Such prolonged action can be a disadvantage, since patients may forget to take a pill which is required only every second or third day.

The mechanism whereby diuretics increase the excretion of potassium involves an increased rate of delivery of sodium and water to the distal tubular site where sodium reabsorption leads to potassium secretion. Any diuretic agent that blocks reabsorption proximal to this distal tubular site has the potential to increase the secretion and excretion of potassium. Furosemide, ethacrynic acid and all the thiazides interfere with sodium reabsorption in the ascending limb, proximal to the distal tubular site of potassium secretion, and thereby lead to increased reabsorption of sodium in "exchange" for secreted potassium.<sup>19</sup> Thus, these agents are associated with increased excretion of both sodium and potassium. Furosemide and ethacrynic acid have been considered to be relatively potassium-sparing drugs since the ratio of excreted sodium to excreted potas-

sium is high. This results entirely from the extensive natriuretic effect of these two agents and not from a sparing of potassium excretion. In absolute terms, renal potassium wasting may be a prominent effect of treatment with furosemide and ethacrynic acid as well as with thiazides.

The extensive natriuretic effect of diuretic agents discussed earlier was determined under optimal experimental conditions, and such power is not encountered in most clinical situations. Table 2 lists factors that will reduce the natriuretic effect of diuretic agents.<sup>19</sup> A reduced GFR will decrease the amount of sodium presented for tubular reabsorption and, therefore, the amount of sodium that can be blocked from reabsorption by a diuretic. Filtration rate is often reduced in diseases characterized by edema. Moreover, filtration rate may fall further as a result of previous diuresis and contraction of ECF volume.

A second factor limiting diuretic activity is that diseases characterized by edema formation appear to be associated with increased fractional sodium reabsorption in the proximal tubules, a site where the diuretic agents exert little or no net effect. Thus, increased proximal sodium reabsorption in edematous states would limit the amount of sodium reaching distal tubular sites where diuretic agents block sodium reabsorption. In the case of organomercurial diuretics, hypochloremic alkalosis limits the pharmacological effect on sodium reabsorption. However, acid-base disturbances have little influence on the action of thiazides, furosemide or ethacrynic acid.

Finally, increased aldosterone activity, common in edematous states, promotes distal tubular reabsorption of sodium in "exchange" for secreted potassium. Thus, diuretics that act proximal to this distal tubular exchange site, may have their natriuretic effect blunted and kaliuretic effect enhanced as sodium is recaptured downstream by aldosterone-stimulated reabsorption.<sup>19</sup> This is the situation in which the aldosterone antagonist, spironolactone, would exhibit greatest natriuretic activity.

Chart 4 illustrates escape from the natriuretic effect of hydrochlorothiazide.<sup>24</sup> This study was performed in a patient with nephrogenic diabetes insipidus, and therefore the concentration of electrolytes in urine was not influenced by fluctuations in changing levels of antidiuretic hormone.<sup>24</sup> On the day the thiazide diuretic was begun there was an increased concentration of electrolytes in

**TABLE 2.—Mechanisms of Escape from the Natriuretic Effects of Diuretic Agents**

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Decreased GFR
Increased Proximal Tubular Reabsorption
Increased Aldosterone Secretion
Enhances Distal Sodium Reabsorption
Enhances Potassium Secretion and Excretion
Hypochloremic Alkalosis
(Mercurial Diuretics Only)

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**TABLE 3.—Some Important Complications of Diuretic Agents**

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Potassium Depletion (Most Agents)
Potassium Retention (Spironolactone, Triamterene)
Hypovolemia (Any Agent)
Decreased GFR, Oliguria
Hyponatremia
Acidosis (Carbonic Anhydrase Inhibitors)
Alkalosis (Most Agents)
Carbohydrate Intolerance (Thiazides, (?) Furosemide)
Hyperuricemia (Most Agents)
Nephrotoxicity (Organomercurials)
Sensitivity Reactions (Any Agent)
Nerve Deafness (Ethacrynic Acid, Furosemide)

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the urine, predominantly resulting from increased sodium concentration. During the ensuing three to four days there was a gradual decrease in the concentration of sodium in the urine without a fall in the total electrolyte concentration. The decreased concentration of sodium was accompanied by an increased concentration of potassium. By the fourth day of diuretic therapy, urinary sodium concentration was below the level present before administration of the drug, and there was a decided increase in potassium concentration. That this reversal of electrolyte composition of the urine was due to increasing aldosterone activity was suggested by the effect of spironolactone to reduce sharply the concentration of potassium and increase the concentration of sodium to similar levels as observed on the first day of thiazide therapy. This is, therefore, a situation in which the use of a combination of diuretic agents is appropriate and effective. It is probably unwise, however, to rely on prepared combinations of thiazides and spironolactone to produce the natriuretic effect illustrated in this example. Instead, the sodium and potassium content of the urine should be examined, and on this basis the decision to add an effective



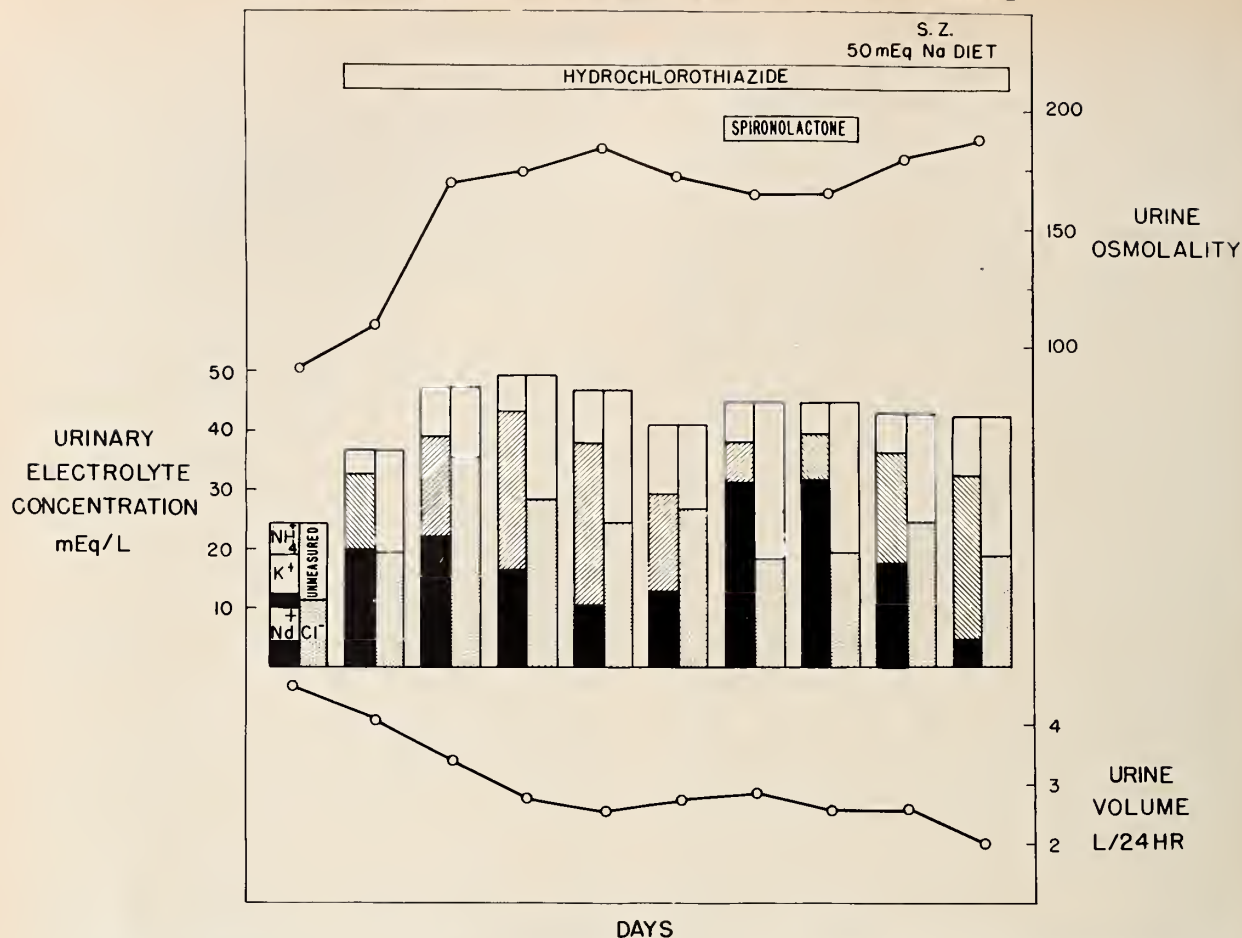


Chart 4.—Attenuation of natriuresis and enhancement of kaliuresis during treatment with hydrochlorothiazide which is reversed by the administration of spironolactone.

dose of spironolactone or triamterine can be made intelligently. If the urinary concentration of potassium is high, the proper dose of spironolactone should increase the concentration of sodium as that of potassium falls.

Before concluding I would like to mention some of the complications of diuretics (Table 3). Except for spironolactone and triamterine, increased excretion of potassium is an almost invariable physiological consequence of diuretic agents. As was mentioned earlier, this effect is due to the increased delivery of sodium and water to the distal potassium secretory site and possibly to an effect of diuresis to simulate aldosterone output.<sup>19,25</sup> Potassium retention and hyperkalemia may complicate therapy with spironolactone or triamterine, agents that specifically interfere with potassium secretion.<sup>23</sup> The proper use of either of these drugs requires the frequent measurement of the serum potassium concentra-

tion. If edema or ascitic fluid is not mobilized in response to diuresis, then hypovolemia may be a major complication of diuretic therapy. Since edema or ascites may persist in the presence of an inadequate intravascular volume, diuretic-induced hypovolemia may not be readily apparent. However, during the course of diuretic therapy a fall in glomerular filtration rate (reflected by a rise in plasma creatinine or urea) and the retention of excess water (reflected by hyponatremia) should be regarded as signs of circulatory inadequacy and indications for discontinuing the diuretic agents.<sup>19,26</sup>

Disturbances of acid-base balance also may occur during treatment with diuretics. Acidosis will result from the use of a carbonic anhydrase inhibitor such as acetazolamide or early in the course of therapy with chlorothiazide.<sup>18</sup> Most of the other useful diuretics increase the excretion of chloride to an extent greater than that of

bicarbonate and as a consequence produce metabolic alkalosis.<sup>26</sup> Potassium depletion, by augmenting tubular hydrogen ion secretion, may contribute to alkalosis. The effect of thiazide diuretics to produce carbohydrate intolerance and worsen diabetes mellitus is familiar to most clinicians,<sup>18</sup> and it appears that furosemide also may have such an effect.<sup>27</sup> Hyperuricemia was originally described as a complication of the thiazide diuretics, but it also occurs with other diuretics. It appears that this may be a nonspecific consequence of diuresis and volume contraction to decrease urate clearance,<sup>28</sup> possibly as a result of enhanced tubular reabsorption.

Except in the case of organomercurials, nephrotoxicity has not been a complication of diuretic agents.<sup>19</sup> However, all diuretic agents, like other drugs, may be associated with sensitivity reactions manifested by hematological, dermatological, or vascular disorders. Pancreatitis has been produced experimentally in animals receiving high doses of certain combinations of thiazide diuretics, and the clinical disease also has been attributed to the agents.<sup>18</sup> When administered in high doses, usually intravenously, ethacrynic acid<sup>29</sup> or furosemide<sup>30</sup> may produce an acute nerve deafness, which appears in most instances to be reversible. Because of the number of potentially dangerous complications of diuretic therapy, the physician caring for patients receiving these drugs should be aware that some of these side effects may preclude achieving the degree of diuresis that may have seemed desirable.

DR. SLEISINGER: Dr. Earley, would you mention the treatment of chloride depletion when one attempts to restore sensitivity to diuretics?

DR. EARLEY: The hypochloremic alkalosis that occurs with diuretic therapy can be corrected by judiciously replacing some of the sodium chloride excreted. Also, other acidifying agents, such as arginine hydrochloride, may be used. Only organomercurials become ineffective in the presence of hypochloremic alkalosis and since we have powerful, orally effective agents, there may be little reason to use organomercurials. Mercurials are potentially nephrotoxic, require parenteral administration, and often cause cramps and other discomforts for the patient. The diuretic

action of thiazides, ethacrynic acid and furosemide seems to be uninfluenced by hypochloremia or alkalosis.

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# Important Advances in Clinical Medicine

## *Epitomes of Progress -- General Surgery*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in General Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Pulmonary Embolectomy

Pulmonary embolectomy, a modification of the Trendelenburg operation now performed under the controlled conditions of cardiopulmonary bypass, is an effective therapeutic tool and survival data is excellent. Its success is dependent upon rapid clinical diagnosis, stressing history and physical examination and adding central venous pressure and electrocardiographic studies as the most used confirmatory tests. The extra time for pulmonary scans may be added if the diagnosis remains in doubt. Pulmonary arteriograms for confirmation are used as a last resort because they greatly increase mortality when pulmonary embolism and right ventricular hypertension with irritability are present. Instrumentation of a distended right ventricle and the addition of a hyperosmolar substance to the vascular system often results in fatal ventricular arrhythmias or intense sinus bradycardias.

Historically, the highest incidence of embolization is in postoperative patients, the second highest in women using birth control pills, and then in the postpartum period. Following embolization, lowered left ventricular outputs result in shock states with poor peripheral perfusion. Cyanosis, hyperventilation and collapsed peripheral veins are noted, while at the same time central venous hypertension is reflected either in the jugular veins or elevated central venous pressure measurements (20 to 30 cm of water). A supraventricular tachyarrhythmia results most likely from the acute right-sided overload. Electrocardiographically, this is atrial fibrillation, atrial flutter, or sinus tachycardia, and these are associated with evidence of right ventricular strain. Arterial blood gas determinations consistently show hypoxemia, hypocarbia and a compensated metabolic acidosis in the form of a normal pH.

Immediate treatment consists of cardiopulmo-

nary resuscitation when necessary, using endotracheal airway and closed chest massage. Intravenous heparin, 2 to 3 mg per kg of body weight, for its antisorotonin and antihistaminic action, and alpha stimulators are mandatory. At times full resuscitation requires partial cardiopulmonary by-pass. Some patients will not require resuscitation, so supportive measures using alpha stimulators are given to increase peripheral resistance against which the fixed left ventricle output may raise the arterial blood pressure. Beta stimulators work against this mechanism and have no suitable pulmonary dilatory effect. Operative intervention is started quickly in patients in whom resuscitation is difficult and for those who do not improve on early medical management. On cardiopulmonary by-pass, a longitudinal main pulmonary arteriotomy is made and thrombus is removed with careful observation of each individual arterial branch. Adequate embolectomy and restoration of normal blood volume eliminates need for further pressor agent administration. Embolectomy is best reserved for the early acute situation, but one wonders if late pulmonary crippling could be reduced by operative treatment for those who slowly improve on medical management. Caval ligation follows closure of the thoracic incision, and in female patients the left renal vein is also ligated.

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### Surgical Management of Coronary Artery Disease and Its Sequelae

The therapy of coronary artery disease has been a controversial matter for decades. Until 1967, direct attack upon the native coronary circulation involved prohibitively high mortality. With the advent of saphenous vein by-pass and inter-position grafts, alleviation of angina, surgically, has become standardized. The long-term follow-up reveals good to excellent results in

greater than 75 percent of patients with only a 5 percent hospital mortality.

Although angina is the more frequent complaint of patients with coronary artery disease, a number of complications due to myocardial infarction are also directly amenable to surgical correction. These include ventricular aneurysms, post infarction ventricular septal defects, mitral valve incompetence, heart block and, more recently, excision of acute infarcts that result in life-threatening arrhythmias or cardiogenic shock.

The five-year mortality after myocardial infarction and the development of ventricular aneurysm is 80 percent—nearly twice the death rate for myocardial infarction alone. The five-year survival following resection of ventricular aneurysms is 65 percent, certainly a commendable result. Post-infarction ventricular septal defects have always been a concern in surgical therapy because of the suturing of necrotic muscle. Recent studies by Iben and others have shown clearly that aggressive therapy can close post-infarction ventricular septal defects successfully during the acute phase. The present hospital mortality of 70 percent in two weeks following the development of ventricular septal defects after myocardial infarction can now be greatly reduced with such maneuvers as "sandwich patch" to the damaged ventricular septum. Mitral valve incompetence from chordal or papillary muscle disruption produces a horrendous state of congestive failure superimposed on already compromised ventricle following an infarction. Replacement by prosthetic or homograft valve certainly is capable of increasing the survival from its present 20 percent in two weeks to more than 80 percent. The late development of mitral insufficiency secondary to displacement of papillary muscles by involvement in the ventricular aneurysms or akinetic segments of the myocardium can certainly be included in the group of patients considered for operative attack. Heart block, which will occur in 3 to 5 percent of patients following myocardial infarction, need only be treated surgically in less than 0.5 percent because of the transient nature of the ischemically induced heart block. Transvenous pacing has reduced the mortality of such therapy to less than 0.5 percent.

Acute infarction resulting in cardiogenic shock or unrelenting arrhythmias is no longer a contraindication for cardiac surgical management. The presence of such pump failure involves joint



management by both medical and surgical means if increased survival of patients with cardiogenic shock is to be expected.

In all cases of surgical approaches to the sequelae of myocardial infarction, exacting studies including coronary arteriography and cardiac catheterization are mandatory to assess the need not only for removal of aneurysms or repair of septae or valves, but for delineating the extent of the underlying coronary arterial disease for treatment.

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### Valve Replacement

It seems quite obvious that the tendency should be to the physiologic where cardiac valve replacement is concerned. Prosthetic valve substitutes have been used over a ten-year period and have done adequately. Their most significant drawbacks are thrombo-embolism (40-50 percent incidence in five years), mechanical failure, ball variance, and the need for constant use of oral anticoagulants. Commendable persistent valve improvement and adjuncts to anticoagulant programs have helped but not significantly over the long-term follow-up.

Non-physiologic homograft preparations, freeze dried, beta propiolactone fixed, irradiated, etc., reduced these tissues to simple non-viable foreign bodies which do not withstand the trauma of blood flow and the test of time.

The viable, sterile, fresh state aortic valve allograft may be placed freehand in the aortic area or sewed onto a valve support ring and used in all intracardiac valve positions. Anticoagulants are required for only six weeks, a time when all exposed fabric is covered by neoendothelium. The function surpasses the prosthesis by showing

less orifice gradient. Thrombo-embolism incidence may be extrapolated to 2 percent in 30 years. Tissue valve procurement is at times made difficult by controlling authorities. Sterility of the tissue is easily obtained. Rejection, if it does occur at all, is of no hemodynamic consequence.

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Angell WW, Stinson EB, Iben AB, et al: Multiple valve replacement with fresh aortic homograft. *J Thorac Cardiovasc Surg* 56:323-332, 1968

### Intravenous Hyperalimentation

The nutritional maintenance of patients for protracted periods exclusively by intravenous alimentation is now becoming an accepted and routine therapeutic measure. Indications for the hyperalimentation regime have extended from patients with severe alimentary disabilities (e.g., massive resections, obstructing lesions, inflammatory disease) to a host of debilitating illnesses (fistulas, extensive burns, massive infections) whose metabolic demands very often exceed the capacity of the normal alimentary route. The recognition of the need for careful skin preparation and for sterile technique during catheter insertion has established infraclavicular percutaneous subclavian catheterization as a safe and effective route for long-term central venous infusions.

The basic nutrient solution consisting of 20 percent glucose and 5 percent fibrin hydrolysate satisfies the requirement of 150 calories per gram of nitrogen needed for proper utilization and protein synthesis. Other necessary additives are 50 mEq of sodium chloride and at least 40 mEq of potassium chloride per liter, together with multivitamin preparations. Magnesium (4 to 8 mEq per day) is a frequent requirement, as are calcium and phosphorus which should be supplied when serum levels indicate early depletion. Though very often supplied by plasma or blood transfusions, trace minerals such as zinc, cobalt, copper

and manganese need to be provided when alimentation exceeds 30 days.

Modifications of this basic regime will undoubtedly lead to more effective maintenance of patients in hepatic failure, renal failure and other frustrating metabolic challenges.

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### Intestinal Atresia as a Complication of Intrauterine Disease Processes

Congenital jejunoileal atresia has been observed with increasing frequency in association with meconium ileus (mucoviscidosis), gastroschisis, ruptured omphalocele, aganglionosis (Hirschsprung's disease) and meconium peritonitis of unknown cause.

All known human forms of jejunoileal atresia and stenosis—that is, (a) "diaphragms," (b) "cord-like tubes" and (c) complete separations (with mesenteric defects)—have been produced in experimental animals (dog, sheep and rabbit) by intrauterine vascular occlusion. Variation in the timing and site of the vascular interruption produces the different types of atresia noted above.

It appears probable that all forms of atresia below the duodenum are the result of vascular "accidents" occurring in the latter stages of pregnancy. When atresia is regarded as a "secondary" phenomenon or "complication," there is increased interest in searching for the basic disease process involved. In addition to the diagnoses listed above, which may produce 25 percent of all jejunoileal atresias in humans, there has been increased recognition of the presence of scars and granulomas of the mesentery (40 percent), and vascular impairment proximal and distal to the site of atresia.

One practical result of the acceptance of this etiologic concept has been recognition of the importance of wide resection in atresia. Whether one believes that this is necessary because of di-

minished blood supply to the intestine proximal and distal to the area, associated with the original infarction, or is because dilatation of the proximal segment has reduced its motility, it is now apparent that a wide resection of the jejunum greatly improves the results of operation. This should be extended proximal to a point of non-dilated intestine.

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### Subphrenic Abscess

Purulent collections above and below the liver, in the lesser sac and beneath the left diaphragm, occur simultaneously in more than one location in 12 to 45 percent of patients. The incidence of missed abscesses varies from 22 to 29 percent and the death rate of patients with multiple, bilateral or missed abscesses is remarkably high, with inadequate drainage responsible for about half the deaths. Traditionally, subphrenic abscesses have been approached by a variety of operations designed to avoid serous cavities in the apparently mistaken belief that the resulting morbidity and mortality rates would be lower. Evidence is accumulating that these "selective" drainage approaches are inadequate, often miss important purulent collections and simply do not work. Formal exploratory laparotomy with drainage that is truly dependent offers substantially improved morbidity and mortality rates, significantly lower incidence of missed or inadequately drained abscesses and appear to be a definite advance in surgical treatment.

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## Current Results with Renal Transplantation—Related Donors

The expected five-year survival rate of renal grafts from related donors is about 75 percent. Two-thirds of the patients are rated as "completely normal" in socio-economic activities. This success is probably accounted for by greater clinical expertise in immunosuppression. The failures are caused mainly by (a) technical errors with the vascular anastomoses, (b) avascular necrosis of the distal ureter, (c) complications of general immunosuppression due to opportunistic infections, (d) abdominal catastrophe secondary to high dose steroid treatment, and (e) hyperacute rejection in presensitized recipients with false negative crossmatch for antibodies against donor antigens.

The basic immunosuppressant drug is azathioprine, a derivative of 6-mercaptopurine, an inhibitor of nucleic acid synthesis. A large variety of drugs or methods are used adjunctively to sustain lower, non-bone marrow suppressant doses of azathioprine. The major techniques are sustained oral prednisone, intermittent systemic steroids and heterologous (usually horse) anti-human lymphocyte globulin (HAHLG). Some centers continue to utilize irradiation of the graft or thoracic duct cannulation. Regardless of the techniques used, the same promising results are obtained with grafts from related donors by both small and large transplant centers.

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## Renal Transplantation—Cadaveric Donor

Despite immunosuppressive techniques identical to those with related donors, the average survival of grafts from cadaveric donors is 40 percent at two years. The excess loss (as compared with related donors) occurs within the first three months. Three important differences exist between related and non-related donor transplants. One is the greater incidence of anuria or oliguria of acute tubular necrosis. Only one year ago some

70 percent of patients receiving cadaveric grafts required hemodialysis following transplantation. Early graft failure was reversible in about half the cases. Transplant centers in California follow three different approaches to the problem. The team at Stanford utilizes kidneys from neurologically-defined cadavers; physiologically normal cardiac and renal function is maintained until the time of nephrectomy. At University of California, San Francisco, renal function is preserved with extracorporeal perfusion with a membrane oxygenator (Belzer perfusion apparatus) up to 24 hours after nephrectomy; poorly perfused organs are not transplanted. In the participating hospitals of the Greater Los Angeles Transplant Society reliance is put upon initial perfusion and subsequent storage in ice until transplantation. Organs obtained from brain-death cadavers do not show early renal failure. Similarly, utilization of kidneys with good *in vitro* perfusion characteristics has reduced the need for early post-transplant dialysis to between 10 and 20 percent.

Another cause of early graft failure is antibody-mediated damage in presensitized recipients. High levels of antibodies cytotoxic to donor cells result in "hyperacute" rejection. Antibodies to transplantation antigens accumulate on the endothelial surface of the intrarenal vessels leading to thrombosis within minutes of grafting. This catastrophe can be predicted by simple screening tests for such harmful antibodies, in effect, a crossmatch of recipient serum with donor cells. However, the most commonly used test, based on cytotoxicity, has about 20 to 30 percent false-negative results. Recently, a more sensitive test, based on binding of antibody to transplantation antigens on cell surfaces, has been developed. This has shown that lesser grades of renal dysfunction (progressive oliguria, high output failure), previously ascribed to acute tubular necrosis (ATN), were in fact associated with lower titers of cytotoxic antibody. Recipients with a positive crossmatch with a donor should not be transplanted.

The exact mechanism of presensitization is unclear. Although blood transfusions during maintenance hemodialysis seem to be the most likely route of sensitization, there is no correlation with the number of units transfused, and only poor correlation with the duration of dialysis before transplantation. Since there is cross reactivity between certain bacterial surface antigens and hu-

man transplantation antigens, sensitization may represent a complicated phenomenon where the antigenicity of white cells are augmented by A-v shunt infections or "dialysis fevers." Early data suggest that institutional dialysis is accompanied by greater presensitization than home dialysis. Presensitization can be diminished by using leukocyte-poor blood and minimizing transfusions while awaiting transplantation.

The third difference between cadaveric and related donor grafts is the greater degree of tissue incompatibility. Initial hopes that improved techniques of tissue typing would provide for better matching of recipient and donor have not been realized; there is no correlation of survival of cadaveric grafts with the number of antigens mismatched. This is not a refutation of basic laws of transplantation immunity, but a reflection of the therapeutic effects of current immunosuppressants: centers utilizing anti-lymphocyte globulin (ALG) show no correlation with typing; those using less effective agents in cadaveric grafts still show slight differences.

Some centers report significantly higher average survival of cadaveric grafts (80 to 90 percent). These observe the following principles: (1) Minimize the period of recipient hemodialysis; (2) screen donors by sensitive assays for antibody to transplantation antigens; (3) use neurologically defined cadavers or perfusion with a Belzer apparatus; and (4) use heterologous anti-human lymphocyte globulin (HAHLG) as immunosuppressant. Long-term results are yet to be evaluated.

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### Renal Transplantation—Types and Mechanisms of "Rejection"

Irreversible damage to the transplanted kidney can occur in three clinical settings, varying both in time and in pathophysiologic pathways. In the

immediate postoperative period, anuria is an ominous sign indicating either technical problems or "hyperacute" rejection. Substantial evidence indicates that the latter is caused by antibodies to transplantation antigens detectable by cytotoxic or binding-inhibition assays in the recipient before transplantation. Minutes after anastomosis of the vessels, there is endothelial and perivascular accumulation of antibody, complement, polymorphonuclear granulocytes and platelets. The platelets and polymorphonuclear cells release locally acting vaso-constrictive factors and enzymes, leading to extensive thrombosis of renal capillaries and ultimate renal cortical necrosis. These factors are not inhibited by immunosuppressant therapy. Attempts at prevention, based on anticoagulation or de complementation, have shown only sporadic success. Today patients of this order should be identified preoperatively and transplantation not done.

The classic cell-mediated rejection begins about five to ten days after transplantation; mononuclear cells (plasma cells, "activated" lymphocytes) infiltrate the renal interstitium, causing local edema and ischemia. Clinically, acute rejection is characterized by fever, malaise, tenderness in the graft; and renal function diminishes. The crises are episodic, respond to anti-inflammatory agents (prednisone), nucleic acid inhibitors (azathioprine, actinomycin D) or agents destroying lymphocytes (HAHLG). Great clinical skill has been acquired in the use of drugs to reverse rejection of this type without causing overdosage and death from opportunistic infections.

"Late" or "chronic" rejection are catch-words to label late failure of the graft. All grafts, regardless of clinical function, show some histologic abnormality on biopsy several years later. Late biopsy typically shows membranous or proliferative glomerulonephritis, as well as interstitial fibrosis and inflammation. Much, if not all, of the damage is due to an immunologic reaction, but the antigen is not necessarily the one causing early rejection crises. Glomerulonephritis in the original kidneys probably has two causative mechanisms: one, antibodies against the glomerular basement membrane (GBM); and two, soluble antigen-antibody complexes hemodynamically deposited in the glomerulus. The antigens involved in immune complex disease are rarely identified; they may be viral coat protein since many cases of nephritis follow an upper respira-



tory infection. These immune complexes, having destroyed the original kidneys, may act in similar manner on the transplanted kidney. Equally possible is the formation of immune complexes to antigens acquired after transplantation. Antigens may be new viral antigens, solubilized transplantation antigens or intracellular renal antigens released by mononuclear cell reaction—the latter being an “auto-immune” disease of the transplanted kidney. Support for this causal mechanism is the high percentage of late failures in transplants from identical twins; ten of 17 patients had recurrent nephritis by the fifth year. These patients, thought not to be at risk from transplant immunity, received no immunosuppression. Results with related donor treated with immunosuppression have better survival, but show similar nephritic lesions on biopsy. What is the best long-term treatment protocol to prevent this late failure? An answer is unavailable. The transplant survival is offered in five- to ten-year projected rates. In all likelihood, the kidneys will not last the lifetime of the individual. This will result in a formidable task to retransplant or dialyze in these cases of graft failure in the near future.

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### Specific Immunosuppression— Enhancement or Immunologic Tolerance

Current methods of immunosuppression are general, inhibiting helpful immune reactions as well as the harmful ones associated with rejection. Two immunologic mechanisms for specific immunosuppression have been known for years but never applied to vascularized organ grafts. *Immunological tolerance* may be produced by pre-treatment with donor antigen *in utero*, in the perinatal period, or, with some antigens, during adult life. Tolerance is thought to represent the removal of all immunocompetent cells which would

recognize the antigen as “foreign.” Once tolerance is induced, recipients will accept any graft from the donor. *Enhancement* of graft survival is produced by the passive administration of antibodies to donor antigens at the time of transplantation. In contrast to tolerance, enhanced survival is limited to that specific graft. Transplantation of a second graft from the same donor at a later time will result in unaltered rejection. *Enhancement* may be established actively by immunization of the recipient with donor antigen so that only “enhancing” antibodies are formed. Current immunologic speculation is that both tolerance and active enhancement may actually be manifestations of the same mechanism—an antibody mediated suppression of the immune response. Successful clinical application of this principle is the elimination of hemolytic disease of the newborn due to Rh incompatibility by treatment of Rh negative mothers with anti-Rh<sub>0</sub>(D) immune globulin.

Kidney transplants exchanged between certain strains of rats will survive indefinitely if treated only four times with enhancing antibody. Control animals die within two weeks. As early as 24 hours after simultaneous grafting and treatment with anti-donor globulin, donor antigens disappear from the endothelial surface of the renal vessels. Three explanations are possible: (1) Enhancing antibody damages endothelial cells in such a fashion that they are replaced by host endothelium. (2) Alternatively, enhancing antibody coats endothelial antigens, preventing their recognition as foreign by host cells. (3) The enhancing antibody may combine with transplantation antigens and remove them from the cell surface. Clinical application of enhancing antibodies (human anti-human transplantation antigen) is awaiting development of purification of the human transplantation antigens, chemical separation of enhancing from cytotoxic antibodies and immunization schedules to achieve high protective-cytotoxic ratios. Investigations along these lines offer the best hope for immunosuppression specific to the donor antigen.

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## Heart Transplantation

The surgery of heart transplantation became practical in man with developments in three fields: (1) safe cardiopulmonary by-pass, (2) adequate myocardial protection during obligatory cardiac anoxia and (3) a surgical technique allowing rapid implantation of the donor heart. Such operations have been performed in experimental animals with an operative survival of 85 percent since first introduced in 1960. It was next demonstrated that denervating the heart by transplantation did not result in congestive heart failure in the absence of immunologic problems. This was followed by discovering means of identifying and treating cardiac rejection. Diminution of the RS magnitude heralds death from rejection in dogs (and now confirmed in man). Treatment with large doses of azathioprine and methylprednisolone would reverse the rejection in many instances and was associated with a rise in RS magnitude. Prolonged survival following heart transplants in dogs and renal transplants in man indicated that clinical trial of heart transplantation in man was justified in a totally incapacitated cardiac patient facing imminent death.

Approximately 160 heart transplants have now been performed worldwide with widely diverse conclusions as to the merit of the procedure. However, in the largest series of transplants, nine of 26 patients operated on over a three-year period are alive and out of the hospital, the longest now more than two years. The one-year survival is 35 percent and improving. Cardiac catheterization at one and two years indicates normal pressures and flows at rest with a two-and-a-half-fold increase in output with moderate exercise. In an alternate series of 12 patients accepted for transplant but not operated upon, the mean survival was 27 days and the longest survival was less than three months. Therefore, heart transplantation is now indicated for relatively young patients in cardiogenic shock or in a wider range of patients with myocardial disease and advanced congestive heart failure. The contraindications are concurrent infection, high fixed pulmonary vascular resistance, diabetes requiring insulin, or primary renal disease.

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## Hepatic Transplantation

Clinical hepatic transplantation has not advanced as fast as kidney grafting for several reasons, the main one being the lack of effective supportive treatment for hepatic failure and the greater technical difficulties of liver transplantation. Immunosuppression is similar to that used in renal transplantation—azathioprine, steroids and heterologous antilymphocyte globulin. The results of clinical liver transplantation are still very unsatisfying. There have been 109 orthotopic liver transplants, 28 patients survived more than one month, 13 more than six months, six more than a year, and three more than two years. Indications for liver transplantation have not yet been defined. Primary hepatocarcinoma has been a frequent indication; however, the three longest survivors (each living at least one year after grafting) died with carcinomatosis. Biliary atresia is another frequent indication; Starzl (University of Colorado) has two patients surviving to 22 and 27 months post-transplantation. However, often unstated is the fact that these children have spent more than 90 percent of the post-transplant period in hospital. Still another indication is hepatic necrosis due to acute fulminant hepatitis. One patient in whom transplant was done because of Australia antigen associated hepatitis has not had a recurrence of either hepatitis or Australia antigenemia at six months. These results show that liver transplantation can prolong life, but that continuous and intensive medical care is required thereafter. Furthermore, the effectiveness of this mode of treatment for hepatic cancer can not yet be evaluated.

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## Transplantation of Other Organs

Transplantation of lung, pancreas and small bowel has been sporadically attempted in several centers, utilizing the principles so successful in renal transplantation. Twenty-four lung transplants have been done (by 18 teams); there are



no functioning grafts (longest survival was ten months).

Nineteen pancreatico-duodenal grafts have been placed (by eight transplant teams), with three functioning grafts, the longest being for 12 months. Recipients usually had juvenile onset diabetes mellitus and renal failure and received concurrent cadaveric renal grafts. The pancreas functioned immediately, and there is little evidence to suggest pancreatic failure with rejection. Patient death has been usually associated with renal failure. One death attributable to the pancreatico-duodenal graft was due to acute perforation of the duodenal portion. These studies indicate that the pancreas is less antigenic than the kidney and suggest that pancreatico-duodenal grafts alone be done for juvenile onset diabetes without terminal nephropathy. If the characteristic vascular lesion of diabetes mellitus can be altered by such a pancreatic graft, then this will become one of the most commonly performed transplant procedures.

The number of transplants of small bowel attempted because of complications of intraperitoneal perforation and infection is less than ten. The longest survival to date has been 26 days. A new approach is to insert a six-foot jejunal-ileal segment subcutaneously between the pylorus and cecum. This exteriorization permits more precise monitoring of the graft without need of repeated laparotomy and decreases the risk of perforation and infection.

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## Hepatitis in Patients Undergoing Hemodialysis or Transplantation

Patients undergoing hemodialysis have long been known to risk getting serum hepatitis because of their recurrent transfusion requirements. The exact magnitude of this risk was not clear until the development of an immunoassay for the hepatitis-associated antigen (HAA, Australia antigen, serum hepatitis antigen) and its association with serum hepatitis.

Epidemics of clinical serum hepatitis among the healthy staff of dialysis centers have now been traced to asymptomatic, HAA-positive dialysis patients. Clinical and laboratory features of hepatitis in these two patient groups are different. In previously healthy staff, an acute disease developed, characterized by serum bilirubin over 3 mg per 100 ml, SGPT over 1000 units and duration of elevated SGPT and HAA-titers of less than ten weeks. The patients on dialysis manifest a chronic anicteric disease, with little or no elevation of serum transaminases, and prolonged persistence of positive HAA titers.

Recently fourteen patients have received renal transplants while carrying the HAA. Immunosuppression did not convert these cases into fulminant hepatitis; all patients had either subclinical or mild clinical disease. However, HA antigenemia continues in all. These carriers have been responsible for eight clinical infections in family members. HAA can be transmitted by the oral, fecal or urine routes as well as by blood. Prophylactic hyperimmune human gamma globulin has not proven effective against accidental needle punctures.

Serial hepatic biopsy studies over 12 months show no signs suggestive of progressive hepatitis. However, the late effects of continued antigenemia in immunosuppressed patients is unknown. The epidemiologic consequences of converting patients on hemodialysis into socio-economically rehabilitated, asymptomatic carriers is a formidable one.

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## Amebiasis

AMEBIASIS CONTINUES TO APPEAR in California. Some infections are acquired within the United States and reflect a continued low level of transmission of the parasite; others are acquired in endemic areas abroad. The two articles on the disease in this issue of CALIFORNIA MEDICINE and two others recently published that review cases seen in California<sup>1,2</sup> attest the need for physicians to remain cognizant of this infrequent but still present infection.

Although amebiasis is a reportable disease in California, the 332 cases recorded in 1969 represent an unknown fraction of the total cases recognized by physicians here. The prevalence of unrecognized infections in the general population of the United States may be as high as 2 to 6 percent, as Burrows suggested in 1961,<sup>3</sup> and 2 to 4 percent in the northern states; but this figure should be viewed with scepticism because of the difficulties he had in appraising data from multiple surveys in the United States, in which techniques of stool examination, expertise of examiners, and the criteria used to distinguish between pathogenic and non-pathogenic *Entamoeba histolytica* varied from survey to survey. Nevertheless, there will be foci in this country where the prevalence rates are higher than these figures suggest because of poverty and poor hygiene or among recent immigrants from endemic areas.

In this issue Doctors Barrett-Connor (page 1) and Turner et al (page 44) discuss three fairly recent important advances in the area of clinical amebiasis. These are the use of metronidazole (Flagyl®) for treatment, the use of serologic methods to facilitate diagnosis, and the use of radioisotope scanning techniques of the liver for diagnosing and localizing liver abscesses.

Metronidazole is a unique drug: it is the first preparation that is highly effective against *Entamoeba histolytica* at the multiple sites the parasite may inhabit (intestinal lumen, intestinal wall, and extra-intestinal tissues) and that causes no serious toxicity for patients of any age.<sup>4,5</sup> This development makes unnecessary the concurrent or sequential treatment of amebiasis with several drugs, some of which occasionally produce severe toxic reactions. Metronidazole has become the drug of choice in many countries for the treatment of severe intestinal disease, liver abscess, ameboma and other forms of extra-intestinal amebiasis, and many authorities in the United States believe it should be the drug of choice here. It may also become the drug of choice for the treatment of asymptomatic and mild intestinal amebic infections and possibly for chemoprophylaxis and mass chemotherapy, but there are few published reports establishing its efficacy, dosage and safety for these purposes.

It is essential that the Food and Drug Administration rapidly complete its appraisal of metronidazole for use in the United States against amebiasis. The application has already been pending for a year. At present the drug is approved only for trichomoniasis at about one-third the dosage employed for amebic infections. If necessary, the manufacturer (Searle) should expedite any additional investigations suggested to meet United States safety regulations for new drugs, so that metronidazole can also become available for the treatment of amebiasis.

A second major advance has been the development of sensitive and specific methods for the serologic diagnosis of amebiasis.<sup>6</sup> The indirect hemagglutination test, a favorite technique, is conducted by the Parasitic Disease Laboratory, Center for Disease Control, U.S. Public Health Service, Atlanta, Georgia, and by some research laboratories, but not by local laboratories. As discussed by Doctor Lewis in the paper by Turner et al, the great usefulness of the test lies in

its ability to diagnose invasive *Entamoeba histolytica* infections. However, the test does not discriminate well between present and recently cured infections and, therefore, does not aid in evaluating treatment. In addition, the test is not sensitive in detecting asymptomatic or mild intestinal infections.

Despite recent advances in our knowledge of amebiasis, problems remain, the solutions of which are important for clinical care. Important needs are: (1) to develop a commercially available antigen that will permit local laboratories to conduct the indirect hemagglutination test; (2) to develop more sensitive methods for detecting intestinal infections and to improve methods that will assist inexperienced technicians in differentiating pathogenic from non-pathogenic amebae; and (3) to establish the safety and efficacy of a prophylactic drug for amebiasis to be used by travelers abroad (at present no drug can be recommended with confidence).

For additional views on amebiasis, see the very fine clinical monograph by Wilmot<sup>7</sup> and the recent review article on the epidemiology of amebiasis by Elsdon-Dew.<sup>8</sup>

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## New Knowledge of Calcium Homeostasis—Advance of a Once Backward Field

THE PAST DECADE has been one of such major advance of biomedical knowledge that half or more of what is known in almost any field was learned since 1960. Although not all of these

advances can apply to medical practice, the input from research into improved diagnosis and management has been rapid and has greatly increased the power of the practitioner to deal with disease.

One example of the magnitude of the change that has occurred is admirably illustrated by the two-part article beginning in this issue, in which Kleeman, Massry and Coburn review the present state of knowledge of and concepts about the physiology of calcium homeostasis. This is a comprehensive review, starting in each case with the simplest background and moving forward, at a pace that readers who have no previous familiarity with the field may find something of a challenge, to the most recent developments at the forefront of research and clinical application. Therefore, it illustrates the rapid pace of knowledge in this field to note that of the 203 references listed, most of which are well chosen, fully 45 percent were published in 1969 or 1970 and only nine percent were published before 1960.

The fact is that, in the late 1950's, calcium homeostasis did not appear to be a very exciting topic and the opinion of most at that time was that the major important knowledge about it already was at hand. Bone was looked upon as metabolically a rather inert tissue which influenced calcium homeostasis mainly through a thermodynamic reaction between its mineral phase and body fluids to maintain a constant ion product of calcium and phosphorous in blood. Parathyroid hormone generally was thought to act on renal tubular reabsorption of phosphate and vitamin D through a stimulation of intestinal absorption of calcium. Estrogen and calcium deficiencies were thought to cause osteoporosis and osteomalacia, respectively.

As we now look on it, these were simple concepts in a field of biology that had been neglected, probably in large part because it is so much more difficult to prepare bone for morphological or biochemical examination than almost any other tissue. This lack of knowledge now is being made up at a pace that is illustrated by developments since 1960, as discussed in the review in this issue. A few of these advances of the past decade are noted below:

- Parathyroid hormone has been isolated, purified, its amino acid composition deter-



mined and the sequence largely solved. It has been established that parathyroid hormone acts at several sites—to stimulate osteoclastic bone resorption, to increase intestinal absorption and renal tubular reabsorption of calcium as well as to increase phosphate excretion. The mechanism of action has been shown to be through activation of adenylyl cyclase. Albright's hypothesis that patients with pseudo-hypoparathyroidism are resistant to parathyroid hormone has been validated by the demonstration that the normal increase in cyclic AMP excretion does not occur in such patients after an injection of hormone. A sensitive radio-immunological assay has been developed which will measure the hormone concentration in normal blood and has been used to show that a substantial number of lung and other tumors secrete parathyroid hormone and that this is a common cause of hypercalcemia.

- Evidence for a second calcium-regulating hormone, not even suspected in the 1950's, was obtained; the hormone calcitonin has been isolated from several species, its cells of origin, mechanism of release and site of action determined; its structure has been determined and it has been synthesized. Medullary carcinoma of the thyroid has been identified as a tumor of its cells of origin and found to secrete this hormone.
- Vitamin D has been shown to act on bone, an excess stimulating bone resorption and a deficiency resulting in inadequate bone resorption and failure to respond to parathyroid hormone. Powerful chemical methods have been developed and used to study vitamin D metabolism. It has been found that a hydroxylated metabolite normally is produced in the liver and that this is the substance that is primarily active upon the target organs. Preliminary studies have implicated abnormalities in this metabolic conversion of vitamin D to its 25-OH metabolite as the cause of hypercalcemia in sarcoid and of osteomalacia in renal disease and some congenital forms of rickets.
- The mechanism of calcium absorption, and presumably of accumulation of calcium ions in cells of other tissues, has come under powerful attack and several steps in this process have been elucidated. Two substances have been found which appear to be connected with this process, a calcium-binding protein and a calcium-dependent ATPase.

- The concentration of phosphorus in blood has been shown to be an important factor controlling osteoclastic bone resorption and responsiveness to parathyroid hormone. A host of other agents have been found to have diverse effects in calcium homeostasis, including glucagon, heparin, epinephrine, theophyllin, mithramycin, magnesium and glucocorticoids.
- Osteoporosis has been found to be very common in older people of both sexes and to be closely inter-related or inseparable from age-related bone loss that affects the entire population. Evidence has been advanced that many factors adversely influence this process, including deficiency of calcium, estrogen, phosphorus and magnesium, and an excess of hydrogen ion, and exercise. The first reliable system for measuring bone mass *in vivo* has recently come into use. Evaluation of several potential forms of treatment is under way, including calcium, sex steroids, fluoride, phosphorus, diphosphonates and calcitonin, but it is probable that a fundamental advance in management of this state will await better understanding than we now have.

In 1960, it did not seem that there was so much to learn. Now, in 1971, we know we have just scratched the surface and that the really profound advances will come in the future. Those who would learn of the present status in this exciting field are referred to the review article in this issue.

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## Tumor Immunology

THE CONCEPT THAT IMMUNOLOGY might someday provide valuable tools for the diagnosis or therapy of malignant neoplasms is both old and, at its inception, almost unbelievably naive. It drew partly from the belief that cancers represented something new, different, "foreign" to the host, and as such should be rejected in the same fashion that external infectious agents were rejected. It also drew great support from immunologists, who fostered and developed these

"naive" assumptions to gain grant support for their foundling science. Fortunately for immunologists and for the reputation of the agencies which supported them, tumor immunology has become both interesting, and perhaps clinically relevant.

The first major assumption in tumor immunology is that most, if not all, tumors would bear new antigens which appear "foreign" to the host—that is, are not expressed on normal cells. To sum up years of careful experimental work in a few words, this has proven to be true. Virtually every tumor system, whether experimental or clinical, viral-induced or carcinogen-induced or spontaneous, is antigenic to the host within whom it developed. Certain general rules have been developed: (1) An oncogenic virus will induce the same antigen in virtually any cell that it transforms, regardless of histogenic origin, host strain, or even host species; (2) chemical carcinogens give rise to tumors which almost always differ from one another antigenically, even if they arise from the same cell type in genetically identical hosts; (3) many tumors express antigens which are present during an early phase of normal embryogenesis—the so-called carcino-embryonic antigens. It is not clear whether or not rule 3 is different than rule 1, which would call for an unmasking of cryptic embryonal antigens as a result of the process of viral oncogenesis. Most human tumors appear to follow rules 1 and 3.

If most tumors are antigenic, why do so many people die of cancer? Are they all immunological cripples, or has some other complexity led to this unhappy state? It now appears that the latter is true, that these patients are the victims of normal, but competing separate internal immunologic systems. Recent work in the cellular aspects of immunity and transplant rejection has revealed this seemingly inconsistent and dangerous dichotomous immune response. When one deliberately immunizes a host with an appropriate antigen, the host responds with two immunospecific effector mediators—cell-free antibodies and cell bound antibodies. The former circulate freely as immunoglobulins and bind to such antigen-bearing carriers as bacteria and free viruses, and, depending on the immunoglobulin's fine structure, prepare these infectious agents for phagocytosis (opsonization), or activate enzyme systems for direct lysis of the offender (complement-fixation), or create a local, but

intense, inflammatory response, sealing-off the progress of infection.

Unfortunately, none of the above-mentioned effector mechanisms appears to be cytotoxic to tumor cells in large numbers. Tumoricidal functions appear to reside in those immunocytes which bear specific cell-bound antibodies. The exact details of how these immune cells cause tumor cell destruction are as yet unknown. However, it is known that these immune cells require close interaction with the target tumor cells, and that if the tumor cell antigens are somehow covered, the tumor cell is not susceptible to immune cell-mediated destruction. Cell-free antibodies may bind to tumor cell antigenic determinants and mask them from immune cells, ensuring tumor survival in an hostile host.

Thus the paradox is revealed, yet unexplained. Why are any tumors rejected? Why haven't we all died of cancer much earlier? Of what possible selective value can such a mechanism have, to be maintained through millions of years of evolution? The answer to the first two questions lies in the timing: cellular immunity appears *before* antibody synthesis, through antigen-induced clonal expansion of immunocompetent precursor cells. Tumor (or graft) destruction has begun before antibody synthesis is going full swing, each antibody-forming cell, also the result of clonal proliferative expansion, producing and secreting thousands of molecules per second. The evolutionary selective value of such "overkill" by the antibody-synthesizing machinery appears to be as a regulator of the immune response; masking of antigenic determinants prevents a potentially endless round of new cells from being triggered into clonal expansion by antigen.

What are the rational possibilities for clinical tumor immunotherapy or immunodiagnosis? Immunotherapy would require a selective inhibition of host molecular antibody synthesis and an augmentation of cellular immunity. Alternatively, antibodies might be rendered tumoricidal by attachment of radionuclides or cytotoxic enzymes to the appropriate specific immunoglobulins. Immunodiagnosis might depend on the localization of such radioactive antibodies to small metastatic lesions, enabling surgical or radiotherapeutic intervention. Alternatively, the appearance of known tumor antigens might signal the reappearance of a tumor long before other clinical signs are apparent.



It is far more important to emphasize the dangers of immunological intervention at this stage. Transfer of molecular antibodies alone, or "vaccination" with tumor cell preparations, may only prevent host cellular immunity from its immunospecific role, with resultant enhancement of tumor growth. Transfusion of immune lymphocytes from tumor-immunized donors is also inappropriate: One cannot prevent these immune cells from carrying out a multi-system immunological attack against all host tissues—the fatal graft against host response—because we have no way of selecting out the tumoricidal cells. For these and many other reasons, there does not appear to be a clinically acceptable method of cancer immunotherapy at this time, and it shall and should remain under laboratory investigation with animal tumors until some of the above difficulties are resolved.

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## New Directions for RMP

ALTHOUGH FAR FROM PERFECT the Regional Medical Program (RMP) in California has been one of the most successful in the nation. It is perhaps too soon to judge just why this has been so, but one suspects that the thrust of the program and the caliber of the people involved in it may have been important. The thrust, to improve the quality of care delivered locally by applying the most up-to-date knowledge available in the large medical centers, seemed both worthwhile and practical to many. The knowledge was there and those who had it could see an obligation to help get it applied so as to meet locally determined community needs for use of this knowledge. This brought about the participation of persons of the highest caliber from the medical centers, from the health professions and from the communities themselves. The record shows that much has been accomplished and also that the task has by no means been completed.

Elsewhere in this issue Paul Ward, the very able Executive Director of the California Regional Medical Program (CRMP), reports upon new directions for RMP which appear to have been decided *ex cathedra* in Washington, and apparently with little or no input from those who have been working with some success to carry out the original intent of what they thought was a good program. Quite briefly the shift in direction is from quality to quantity in the delivery of services, from the dissemination and application of medical facts to the application and dissemination of health care theory, and from what local communities decide they need and want to what the federal bureaucracy has decided they should have. Since federal funding in health is either granted or withheld according to whatever federal guidelines happen to be current, considerable impetus for the prescribed new directions for RMP may be expected.

It remains to be seen whether the effective instrument which RMP has now become (at least in California) can be so completely redirected in its emphasis by federal fiat, and still be effective or even useful. The strength of CRMP to date has been in the recognized validity of what it sought to do and in its consequent ability to attract competent people in academia, in practice and in communities who have had the knowledge and skills needed to achieve these aims. That there are also unsolved problems and needs in improving the quantity and distribution of medical and health services is certainly not to be denied. But in this case the real knowledge of what to do about it or how to do it does not yet exist, although some who may be in very high places seem to be convinced they have the answers. The fact is that the science of modern health care delivery has hardly begun to develop as compared to modern medical science.

It is suggested that the substitution of assumption, theory and belief with respect to health care delivery for improving the use of existing medical knowledge in patient care may prove to be a fatal weakness in the new directions for RMP. The persons in academia, in practice and in the communities who because of their knowledge and skills have made RMP in California an effective instrument for its original purposes, are not as likely to have the knowledge and skills needed for the new directions for RMP, and further they may often be of the opinion that no one else does

either. If these observations are correct, then the new directions for RMP will require the fashioning of a new kind of instrument, at least in California, which may or may not accomplish the new aims set for it, and which will probably leave unsupported and unfinished much of the worthwhile work which has been undertaken by the program as it has existed until now.

We have considerable confidence in the California Committee on Regional Medical Programs (CCRMP). We hope CCRMP will find ways to adapt the California program to the new directions prescribed in Washington without sacrificing the knowledge and the support of those skilled persons who have been so integral a part of its worthwhile and successful regional and area activities. However, it appears that CCRMP now has been given somewhat of a square peg and directed by Washington to fit it somehow into a round hole. We shall be watching developments with no little interest and with considerable apprehension.

## Of Life Styles and Health Care

THE TERM "LIFE STYLE" has recently come into vogue and has begun to serve a useful purpose. It refers to the ethnic or cultural background, language, education, degree of affluence or poverty and way of life of individuals or groups of citizens. It has been demonstrated frequently that life styles are something to be respected if one is seeking ways to deliver medical and health care services to those who for one reason or another may not have had their share. But life styles are far more important to the realization of goals in health care than has so far been appreciated.

Life styles, in the sense the term is now being used, are not easily changed, or even modified. To impose one life style upon another is not a simple matter, and in a free society it usually just cannot be done. This has been demonstrated many times in rural and urban ghetto

communities where the communities tend not to accept the providers' model of health care delivery and the providers find it equally difficult or impossible to adapt their life style and habits to that of the community.

As one examines this problem it quickly becomes obvious that while some attention (though not enough) is now being paid to the life styles of consumers, very little or none is being given to that of physicians, who after all are among the most essential providers of health care. Physicians too have their indigenous life style. They have their own cultural interests and activities, colleagues with whom they need to associate, wives who are unhappy living in unfamiliar cultural settings, and children who they feel are entitled to as many cultural and educational advantages as they can give them. This sort of life style is just as important to a physician and his family as are the variety of life styles which are indigenous to the consumers of the health care services he provides. Yet somehow these must come together better than they do now if our health care goals are to be realized.

It seems time to begin to recognize the realities of life styles and respect the way of life both of the providers and the recipients of health care. We must not expect any life style suddenly to change completely or abandon its ways to accommodate another. This is part of the pluralism so characteristic of America and it is the genius of America that these pluralisms find ways to live together, work together, communicate and learn from one another. The goal of equal access to high quality health care is shared by all who are aware of the problems. We can now recognize that there is more to achieving this goal than just adequate resources and good economics. These are important, even essential, but so is the need to accomplish what must be done within and among a variety of life styles. We can begin by developing better channels of communication, of action, of feed-back going both ways, and the means for better evaluation of what is actually being achieved, as we work toward the common goals.

These human aspects of health care delivery deserve much more attention than they have so far received from social planning, health care planners, or even physicians for that matter. This *could* be a major challenge for the '70s.



# CASE REPORTS

## Metachronous Development Of Regional Enteritis of the Colon in a Patient with Ulcerative Colitis

RICHARD R. BABB, M.D., AND  
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PATIENTS WITH IDIOPATHIC ulcerative colitis can usually be differentiated from those with regional enteritis (Crohn's disease) of the colon by careful assessment of clinical, sigmoidoscopic, radiographic and pathologic findings.<sup>1-5</sup> Occasionally, however, this distinction is not possible since, as noted by Lennard-Jones et al.,<sup>3</sup> "neither [of the two diseases] has defining features, present in every case of one and absent in every case of the other." Thus, there would appear to be a spectrum of primary inflammatory bowel disease with idiopathic ulcerative colitis at one end, regional enteritis at the other, and a small percentage of unclassifiable or overlap cases in the middle.

Although examples of both diseases in the same patient have been mentioned, such reports have been poorly documented and no pathologic material shown.<sup>6-11</sup> We have recently seen a patient who initially met the criteria for diagnosis of idiopathic ulcerative colitis, and yet four years later returned with an exacerbation of symptoms, ultimately proven to be secondary to regional enteritis of the colon. This progression of one disease into the other in the same patient raises many

questions regarding the nature of primary inflammatory bowel disease, and because of its rarity, is worthy of report.

### Report of a Case

A 27-year-old mechanic first came to the Palo Alto Medical Clinic in April 1965 after suffering with fever, abdominal cramps and bloody diarrhea during the preceding three months. There was no history of recent travel, radiation therapy, venereal disease or previous disorder of connective tissue. The patient's past health had been excellent. The physical examination was normal. Laboratory tests showed a hemoglobin of 11.0 grams per 100 ml, leucocyte count of 17,100 per cu mm, and a sedimentation rate of 55 mm in one hour. Cultures of the stool for pathogenic bacteria and parasites were negative. Sigmoidoscopic examination revealed diffuse hyperemia and granularity of the rectal mucosa. A rectal biopsy showed ulceration of the mucosa, acute inflammatory infiltrate of the mucosal stroma, and crypt abscesses (Figure 1). Roentgenographic examination of the colon with barium (Figure 2) showed diffuse ulceration of the mucosa extending from the rectum to the splenic flexure. The terminal ileum appeared normal. Examination of the stomach and small bowel with barium was normal.

A diagnosis of idiopathic ulcerative colitis was made, and administration of Azulfidine® (salicylazosulfapyridine) was begun, 4 grams a day. Within a few months, the patient had complete cessation of diarrhea and he felt well. He then stopped all medication, and did not return for re-evaluation until May 1969, some four years later.

In March 1969, or six weeks before this revisit, he had once again noted the onset of abdominal cramping, diarrhea, increasing anorexia, and loss of weight. He was having eight to ten liquid, non-bloody stools a day and two to three at night. He had been admitted to hospital elsewhere, and there had been given 30 mg of prednisone each day, with only minimal improvement over a one-week period.

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Submitted May 8, 1970.

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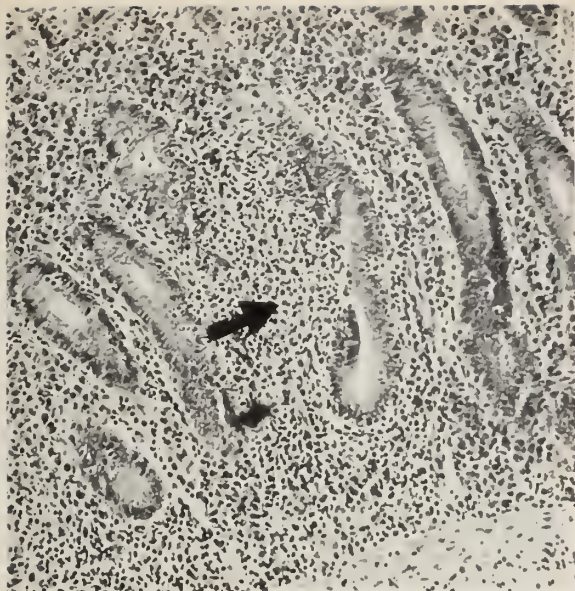


Figure 1.—Rectal biopsy, 1965. Note the diffuse inflammatory infiltrate in the mucosa and the crypt abscess. (Hematoxylin and eosin stain, X40)



Figure 2.—Barium enema roentgenogram in 1965 showing ulceration extending from the rectum to the splenic flexure. The terminal ileum is normal.



Figure 3.—Barium enema roentgenogram in 1969 showing deep ulcerations in the sigmoid, descending and transverse portions of the colon. The rectum and splenic flexure areas appear normal.

At examination he appeared acutely ill. There were signs of intraoral moniliasis, and the abdomen was slightly distended and moderately tender in the lower quadrants. Bowel sounds were present. No other abnormalities were noted. Sigmoidoscopic examination revealed several superficial fissures in the anal area and minimal friability of the rectal mucosa.

Treatment consisted of a milk-free diet, intravenous fluids, 60 mg of prednisone a day, and 40 units of intravenous ACTH a day. Laboratory tests showed hemoglobin of 11.6 grams per 100 ml, packed cell volume 38 percent, leucocytes 8,200 per cu mm and a normal white cell differential. The platelet count was elevated at 571,000 per cu mm. Results of liver function tests, serum electrolytes and magnesium values were within normal limits. The serum albumin was 2.6 grams per 100 ml. Several stools were positive for occult blood. A plain film of the abdomen showed no signs of a toxic megacolon.

Despite the above medical regimen, the patient continued to have severe diarrhea and increasing





Figure 4.—Surgical biopsy of diseased colon 1969. The mucosa is not seen. Note the pronounced transmural inflammation, submucosal edema and fibrosis. (Hematoxylin and eosin, X10)

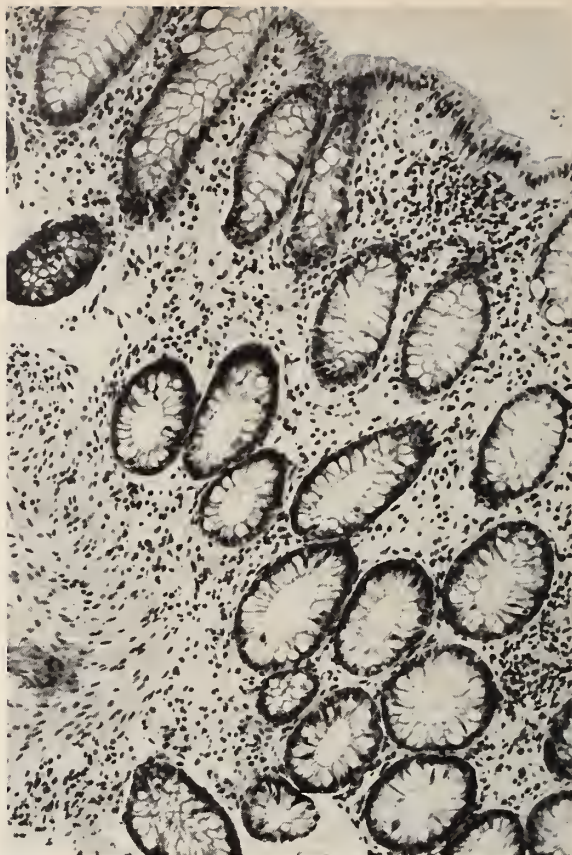


Figure 5.—Rectal biopsy, 1969. The mucosal epithelium, stroma and crypts are normal. (Hematoxylin and eosin stain, X40)

anemia. Transfusion with 5 units of blood was required over the next two weeks to keep the hemoglobin value above 10 grams per 100 ml. Examination of the colon with barium (Figure 3) showed deep and shallow mucosal ulcerations, longitudinal ulcers and a "cobblestone" appearance. The rectum, splenic flexure and portions of the ascending colon were not involved. The interpretation was regional enteritis of the colon. Examination of the stomach and small bowel with barium showed no abnormality.

Because of the persistent debility, anemia and diarrhea, the patient was operated upon three months after his illness began. The colon was found to be thickened and inflamed from the cecum to the sigmoid area. The rectum appeared grossly normal and this was confirmed with sigmoidoscopic examination. A diverting ileostomy was performed.

Biopsy of the colon (Figure 4) showed pronounced transmural inflammation, several micro-

fissures extending downward from the mucosa, submucosal edema and fibrosis, and a chronic serositis. No granulomas were seen. Staining of the biopsy specimen with periodic acid-Schiff and alcian blue showed the mucosal mucin to be well preserved. Rectal biopsy (Figure 5) showed no abnormality. These findings were felt to be consistent with regional enteritis of the colon.

The patient made an uneventful postoperative recovery, and prednisone was gradually discontinued. Over the next six months of observation he remained asymptomatic, regained 30 pounds of weight, and was working full time as an auto mechanic. Laboratory tests showed no anemia and the platelet count was normal.

## Discussion

Patients with ulcerative colitis usually complain of bloody diarrhea. Sigmoidoscopic examination reveals an erythematous, friable, and granular rectal mucosa which, on biopsy, shows a diffuse



mucosal inflammation, and crypt abscesses.<sup>3,12,13</sup> Barium examination discloses continuous ulcerative disease of the colon extending from the rectum upward, and internal fistulae are not seen. At operation the serosa appears normal, and the mucosa shows diffuse ulceration and hyperemia.<sup>1-4</sup> The characteristic histologic appearance is one of mucosal and submucosal inflammation, intense vascularity, many crypt abscesses, and no fissuring or granuloma formation.<sup>3,12,13</sup>

In contradistinction to the above, patients with regional enteritis of the colon commonly note non-bloody diarrhea, and often have a noticeable weight loss.<sup>1-5</sup> An abdominal mass, enterocutaneous fistulae, and perianal fissures or ulcerations may be found. At sigmoidoscopic examination, one may visualize normal rectal mucosa in at least 50 percent of cases.<sup>3</sup> If abnormal, the mucosa may show small discrete "aphthous" ulcers or a cobblestone pattern. Barium examination shows skip areas between areas of pathologic change, a cobblestone pattern, longitudinal ulcerations, deep fissures, internal fistulae and an abnormal small bowel often is seen.<sup>1-3</sup> Grossly, the colon is thickened, and areas of serositis and stenosis are common. Longitudinal and transverse slit ulcers, cobblestoning and lymphedema of the submucosa, interspersed with normal mucosa is seen. Differences from ulcerative colitis in the microscopic sections include transmural inflammation, submucosal fibrosis and marked lymphoid aggregates, linear deep ulcers or fissures, few if any crypt abscesses, and non-caseating granulomas in 30 to 70 percent of cases.<sup>1-3,5,6,14</sup>

By the above criteria, the illness of the patient in the present case began with idiopathic ulcerative colitis: He had bloody diarrhea, diffuse rectal involvement as observed on sigmoidoscopic examination, and characteristic rectal biopsy and radiographic features (Figures 1 and 2). Four years later, however, diarrhea was not grossly bloody. Sigmoidoscopic examination and rectal biopsy were normal (Figure 5). Barium examination of the colon, (Figure 3) and subsequent surgical findings were consistent with regional enteritis of the colon (Figure 4).

We have been unable to find a well-documented case of this progression or metachronous development in the literature. As mentioned in the introduction, several reports have made mention of both diseases concurrently in the same patient, or the development of one after the other. However,

the nosologic terminology in these reports has been confusing. Moreover, many of the patients had had previous bowel operations, and no slides of pathologic material were included.<sup>6-11</sup>

Several groups have now reported cases of primary inflammatory bowel disease which cannot be easily classified into ulcerative colitis or regional enteritis.<sup>15-18</sup> Such examples of "overlap" show a poor correlation between clinical impression and eventual pathologic diagnosis. The exact criteria noted in the opening paragraphs do not always help distinguish these two diseases in the individual case. Clinically the two diseases may be very similar in both colonic and in extracolonic manifestations such as uveitis, skin lesions, arthritis or jaundice.<sup>19</sup> Toxic megacolon<sup>1,20</sup> and carcinoma of the colon<sup>21</sup> have been reported in regional enteritis of the colon as well as in ulcerative colitis. Sigmoidoscopic examination may not always be helpful, as about 5 percent of patients with ulcerative colitis show normal rectal mucosa and those with regional enteritis may have findings indistinguishable from ulcerative colitis.<sup>3,4</sup> Crypt abscesses can be found on rectal biopsy of patients with regional enteritis, and (rarely) granulomas may be seen in ulcerative colitis.<sup>12,13</sup>

Hellerstrom and Fisher<sup>22</sup> reported the estimation of mucosal mucin to be an aid in the differentiation of inflammatory bowel disease. They noted good preservation of the mucin in the regional enteritis of the colon and pronounced reduction of mucin in ulcerative colitis. Later studies<sup>18,23</sup> failed to confirm this finding as a differential aid, however, especially if mucin is present, as it was in the present case. Although immunological mechanisms may be different in the two diseases, Doedhar et al.,<sup>24</sup> using various immunologic techniques were unable to distinguish between the two.

This report was written to emphasize the occasional difficulty in distinguishing ulcerative colitis from regional enteritis of the colon. Although, for reasons noted above, we cannot state with certainty that one disease progressed into the other, it would appear that such was the case.

## Summary

Using accepted clinical, radiological, and pathological criteria, we have presented a patient in whom regional enteritis of the colon developed four years after a diagnosis of idiopathic ulcerative



tive colitis had been made. This apparent progression of one disease into the other points up the occasional difficulty in distinguishing between these two inflammatory bowel disorders.

#### ADDENDUM

In the summer of 1970, or one year after the diverting ileostomy, our patient began to have diarrhea and a mucoid discharge from the rectum. Roentgenographic examination of the colon with barium revealed foreshortening, generalized pseudopolypoid, and mucosal ulceration in the descending colon. The rectum appeared normal, and this was confirmed at sigmoidoscopic examination.

Total colectomy and proctectomy then were performed. Since then, the patient has felt well, and there have been no signs of ileostomy dysfunction.

Microscopic sections of the resected colon showed no evidence of vertical fissuring or granulomas. There were mucosal ulcerations and many crypt abscesses. Mucosa away from the sites of ulceration showed loss of mucin secretion. These findings were compatible with ulcerative colitis.

We feel this sequence of events further underscores the main theme of our report. It may be impossible to classify certain patients with inflammatory bowel disease into a distinct and unchanging category at any given time. On the basis of accepted nosological criteria, our patient evolved from one "disease" to the other and then back again.

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#### CATHETER SITES FOR MONITORING SHOCK

By what route do you insert the catheter if you want to monitor central venous pressure in a patient in shock?

"For the physician or surgeon who is very much at home in the critical care environment, the subclavian route, I think, is a good route. You can get into it rapidly with some skill. You can maintain the catheter away from sites of interference. But, on the other hand, for the occasional operator, that area is fraught with some dangers — namely, pneumothorax, possibility of penetrating the aorta, and so on. So that for the occasional operator, I would prefer seeing the catheter placed by way of the brachial vein."

—MAX HARRY WEIL, M.D., Los Angeles

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# LETTERS *to the Editor*

## Prepare for (the Right) Action

*To the Editor:* In the January issue, Doctor Alan Matzger [Letter to Editor: Where's the Action, January 1971, page 45] asks for guidance on "some troubling issues" because he finds himself "too young to be Establishment and too old to believe in revolution and destruction of institutions." As an older colleague who has concern for the problems of youth, I hope I can help.

Doctor Matzger, you decry the use of a study committee and by so doing flatter your elders if you think they have pat answers to dissatisfactions with health care delivery. Put yourself in the place of a "sincere colleague who sits in a responsible position," e.g., the president of a county medical society, and imagine that a "group of whoevers have just posed a problem." Do you simply smile tolerantly and dismiss the whoevers with the first answer that comes to mind or do you ponder the problem and call on other learned colleagues for their opinion and try to come up with a wise answer for your concerned fellow citizens.

Doctor Matzger, you ridicule calling a conference on hunger when a malnourished child pleads for help. It would be easier to airmail him a doughnut than to study the real problem in a conference. But he will need another doughnut tomorrow. Instead of a hand wringing quest for pat answers, Doctor Matzger, call your

county medical society president and ask him to put you on a committee where your views will be heard and respected. You might find some of the older establishment types in the midst of a revolution.

F. BRUCE KIMBALL, M.D.  
*La Jolla*

## Mid-Trimester Abortions, Fetal Weight and Ethics

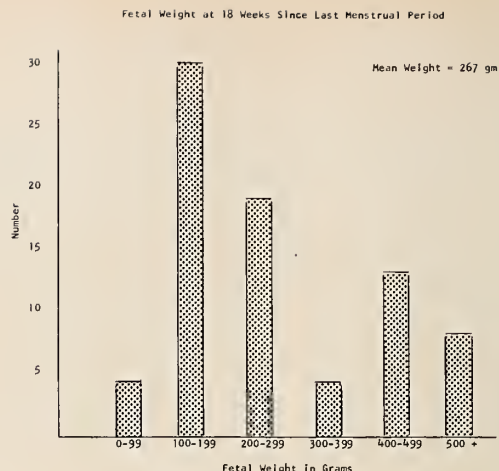
*To the Editor:* Throughout California, physicians with extensive clinical experience have been placed on probation by staffs for performing therapeutic abortions when the fetal weight was greater than an arbitrary value, usually 450 to 500 grams. In the Stanford University Hospital, therapeutic mid-trimester abortions with intra-amniotic hypertonic saline generally are done between the fourteenth and twentieth week of pregnancy. For purposes of fetal weight analysis, pregnancies interrupted during the eighteenth week as calculated from the first day of the last menstrual period were reviewed for the 12-month period ending October 31, 1970, when a total of 394 women were aborted with saline. Seventy-eight of them were said to be in



the eighteenth week and as shown in the accompanying chart, the distribution of fetal weights was very wide. Similar variations of fetal weights occurred during other weeks of pregnancy.

The marked variation in fetal weight for stated weeks of pregnancy observed here suggest either that our obstetricians have found it impossible to accurately determine the duration of mid-trimester pregnancy or that fetuses vary markedly in their weights at specific periods of gestation. Hardwick,<sup>1</sup> like others, found that fetuses in the eighteenth week had a mean weight of 223 grams with a range of 152 to 307 grams, which suggests that our local experience reflects the physician's inability to estimate fetal weight and thus the stage of gestation.

In communities where physicians perform therapeutic abortions on patients seen for the first time in the mid-trimester, it is difficult to estimate the duration of gestation accurately if the patient either is uncertain or lies about the date of her last menstrual period. It therefore seems unreasonable for administrators or hospital staffs to agree to accept patients for mid-



trimester abortions and at the same time set an arbitrary upper limit for fetal weight, particularly if the occasional abortion of a heavier fetus will result in a charge against the obstetrician involved.

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<sup>1</sup>. Hardwick, DF: Weight and length of fetuses in relation to age. *J Reproductive Med* 2:98, 1969

### ANTACIDS IN ULCER THERAPY

"There is so little difference between the various antacids. What's much more important is when they're given. Far too many people give antacids after meals. This is ridiculous. They should be given one hour before a meal or midway between feedings. In that way you cut down the level of acidity and you have a lower peak before the next meal. Never give antacids immediately after food when you've already got its effect cutting the acidity in the stomach. I prefer a mixture of antacids—calcium carbonate, sodium bicarbonate, and magnesium oxide. I think that's better than just a single one. But the time is the important factor."

—F. AVERY JONES, M.D., London

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# The Regional Medical Program in California

## Its Changing Nature

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IN THE EARLY PART of its fifth year of funded support, the California Regional Medical Program (CRMP) is continuing to evolve, to assess its progress, its objectives and its manner of carrying out the philosophy and intent of the legislation authorizing what is in many ways an unusual federal program. Along the way there has been praise for the accomplishments of the California program, due in great part to the strong support in this state from both professionals and laymen in medicine and health; and there have been disappointments.

Changes in program direction have not been limited to California, but have been accelerated by the national Administration's recent adoption of priorities for health and a consequent desire to pursue these enunciated health goals through existing health programs.

The Guidelines for the original legislation establishing regional medical programs (Public Law 89-239) described a major purpose of RMP as a "creative partnership" among practicing physicians, hospitals, medical schools, nurses, public and voluntary health agencies and other health resources. New "cooperative arrangements" in the partnership would help to bring new knowledge more rapidly to the patient's

bedside, no matter where he lived. The attempt was to be made to bring high quality medical care more quickly to every American citizen. As the Guidelines put it, the program was "intended to provide a means for conveying to the medical institutions and professions of the nation the latest advances in medical science for diagnosis, treatment and rehabilitation of patients afflicted with heart disease, cancer, stroke or related diseases." Although preventive medicine was intended as part of these programs, the concept of prevention received strong endorsement in the renewal legislation passed in 1970 toward the close of the Ninety-first Congress. The new law, P. L. 91-515, also adds kidney disease as a categorical emphasis and brings in required participation by the Veterans Administration.

As the Program developed in California, the emphasis was very heavily in favor of categorical interests, and concentrated principally on achieving the desired improvements in health manpower and facilities through regional cooperative arrangements among existing professional and institutional resources, and continuing education. When the recommended national priorities for health were published in the spring of 1970 by the Department of Health, Education and Welfare (DHEW) there emerged a concerted effort to change the general direction of the Program. The emphasis on improving quality of medical services was considerably relaxed, and even to

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some extent discouraged, and the emphasis on improving the quantity of care was greatly increased.

As the Administration prepared to introduce its bill to extend Regional Medical Programs, national leaders began to speak favorably of developing "primary care" in areas where available medical and health services were insufficient to meet local needs. Had the proposed Administration bill passed, it would have eliminated the categorical emphasis of RMP, turning instead toward creation of new health care services and deleting the prohibition against interfering with existing patterns of patient care. Although the new legislation in its final version continued the categorical emphasis with the addition of kidney disease and retained the proscription against interfering with patterns of patient care, leaders in both DHEW and the Office of Management and Budget have recently emphasized the need for the Program to promote "new patterns of medical care" and to engage in the development of new and innovative levels of manpower. They particularly discuss the physician's assistant concept.

Spokesmen for the Administration have also emphasized that RMP should engage in the task of obtaining physician acceptance of the new forms of delivery and should help develop the training programs that would make new levels possible. One of these officials posed this question to the Program: "Is [RMP] providing a vehicle for physician acceptance of new forms of medical practice, such as prepaid group practice or improved referral patterns that may lead to higher quality or less expensive care?" This comment, from a White House aide in the Office of Management and Budget, appeared to some observers to be more of an instruction than a question, and is the only recent context in which the term "higher quality" has appeared. The conclusion seems inescapable: the original purposes of the Program have been altered.

This alteration has unsettled or disturbed some in the Program, both on staff and voluntary levels. Since the planning for operational projects requires a fairly long time, the projects on which planning begins on one day may be inappropriate for the priorities that exist on the day the planning has been completed. And those who

may have joined the Program on a voluntary basis in the beginning, and who have a deep interest in one of the categorical pursuits, may not find the Program to their liking with the implied change in emphasis.

One result is that the Program has had a certain amount of turnover in voluntary participation. In the beginning it attracted those who were deeply interested in the quality of medical care and in the categorical approach to improved health services. Later the Program attracted persons more interested in developing a greater quantity of care, especially for those areas without it today. This change in program direction also required a change in the stated objectives of the California Region.

But there have been other perhaps more subtle influences on RMP program development. The Program began with the expectation that it would eventually be funded at levels as high as \$500 million annually. In view of this expectation, many Regions began to develop plans for an over-all Program that would reflect this level of funding. Core staffs were recruited and began extensive planning pointed toward \$500 million funding levels in the third or fourth year of the Program. This accelerated planning pace could not possibly be rationally maintained when it became clear that available funding support was not expected to be even as much as one-quarter of the originally anticipated amount.

Since RMP effectiveness is built upon voluntary relationships, this unfulfilled commitment also had a retarding effect on the level of participation and enthusiasm as the months wore on. Many volunteers who had been extremely active in the beginning became disenchanted with the slow pace of funding, or the lack of funding, for the projects they had helped to develop. Some withdrew from RMP involvement altogether, or turned to other activities promising less frustration. The uncertainties of Federal funding had a deleterious effect on RMP core staffs as well. Some Areas in California were unable to stabilize their staffs, leading to uneven development in the cooperative arrangements necessary for a dynamic and successful Program. As a result, some Arcas moved faster in developing proposals to meet the needs expressed locally, while others developed more slowly. In the long term this substantial cutback in the expected funding levels for RMP may have been the most damaging

development in terms of progress and success for the Program.

During the earliest meetings of RMP in California, it became apparent that strong feelings of territorial imperatives existed within each Area. Since each Area had been assigned a geographic territory for planning, and since the Area offices were administratively based within the structure of California's eight medical schools, it was natural that there would be healthy competition among the Areas. To a certain extent these feelings were expressed in the process of establishing objectives and goals to meet local needs. But the most prolonged examination of this sensitive subject came at meetings of the California Committee on Regional Medical Programs, particularly when the CCRMP was considering proposals for operational activities. The project review process was clumsy and inequitable and satisfied few. This was perhaps the natural result of a body of so diverse a nature, newly created, trying to gain an understanding of its responsibilities among unfamiliar or unsettling surroundings. The law was a new kind of social legislation. Several of the members of the CCRMP were strangers at first. And certainly most of the members had never sat on a committee where laymen would review medical matters. After two years a special subcommittee was established to review the organization and procedures of the CCRMP. A detailed series of recommendations to improve the technical review of project proposals was developed and finally adopted in October, 1970. The review mechanism now in effect has been thoroughly tested, is well understood throughout the Region, and appears to be well accepted. It has been highly praised nationally.

Establishment of objectives for the California Region also took many months and reflected some of the stress that grew out of the competitive feelings between Areas and between Areas and the Region. The objectives finally agreed upon have enjoyed an unusually high level of input from the voluntary associations, the professions and others interested in the Program. Because of the changing direction of RMP nationally, California has developed two sets of objectives. The first set follows the original intent of the Program, describing concepts and activities intended to lead toward an improved quality of medical and health services, along categorical lines. The second set of California RMP objec-

tives reflects the more recently announced national health priorities, emphasizing more the quantity of services, the development of different levels of manpower and the improvement of the organization and delivery of medical care. Stated another way, the original objectives apply to continuing education for existing health team professionals and for innovation, development and testing of delivery systems of health care or training programs, all extending over a period of years. The newer list of objectives is more modest in cost and scope, intended for shorter projects, in a framework within which demonstration or feasibility projects may be attempted to stimulate change in the organization and delivery of health services, particularly health services for the poor. Although they represent a more modest approach at this time, it would appear that they forecast the dominant course of the Program in the immediate future.

The newer objectives have been agreed upon by the California Committee on Regional Medical Programs in preparation for administrative changes expected to be established for California by the Regional Medical Programs Service of DHEW. The Administration has announced its intent to decentralize as much of the grant-making powers as possible. As part of this move, a limited number of RMP regions which have demonstrated administrative and fiscal management skills, and carry on program activity thought to be worthy of strong support, will be placed on an anniversary review basis. This will mean that requests for operational support funds will be made only once a year, and that the RMP regional advisory group (in California's case the CCRMP) will have greater responsibility for the management and the effective redirecting of available RMP funds within the Region. As part of the anniversary review concept, a developmental component will be awarded for short-term experimental or innovative activities that can be considered and begun after a very brief review period.

The second and more recent set of objectives for California was established for the developmental component. These objectives have two main priorities of equal importance. The first is to stimulate efforts to improve and increase the health manpower pool, focusing on professional,



sub-professional and para-professional personnel. The second is to stimulate change in the organization and delivery of health services, particularly for the urban poor, stressing preventive measures, prepaid group practice, use of sub-professional and para-professional personnel, ambulatory care services and neighborhood care delivery units. Other goals and target groups in the second priority category include improved coordination of Federal, State and local efforts to benefit migrant farm worker families, Indians and children during the first five years of life, and provision of adequate family planning services by 1975 to women of childbearing age who cannot at present obtain or do not have knowledge of such services. Projects of this short-term nature should stimulate the development of proposals for much larger scale efforts to serve the national priorities. Built into these long-term, large-scale efforts should be the eventual reliance on the sources of health care funding traditionally available to communities.

While Federal funding levels have been a disappointment to many, there have been several instances where alternate sources of financial support have been developed as a result of the original stimulus for planning under RMP leadership. Since it does appear that the Administration intends to follow the concept of level funding for Regional Medical Programs during the immediate years ahead, the use of RMP staff time to seek alternate sources of funding will become more important than it has been in the past. A substantial amount of effort is expected to be directed by RMP toward such catalytic activity.

One more indication of change in RMP pro-

gram development is becoming more apparent. In the Fall of 1969 there was the first organized attempt to bring together representatives of RMP offices and Comprehensive Health Planning representatives for the purpose of discussing issues of common interest. From this meeting there developed a more formal effort to define ways in which the two programs could work more closely together. The legislative mandate for Comprehensive Health Planning is far broader than it is for RMP, and the CHP offices throughout the State will be heavily burdened during the coming months with health facilities planning, largely because of California Law A.B. 1341. It has been proposed therefore that RMP assume as much as possible of the CHP responsibility for personal health services and manpower planning. This proposal is being developed with understanding and agreeable relationships among RMP and A and B agency\* representatives of Comprehensive Health Planning. The California Committee on Regional Medical Programs has asked the State Health Planning Council to designate an official representative to be a member of CCRMP, to speak for A agency interests, and is also seeking an official B agency representative. The two programs appear to be meshing with a realistic appreciation of the responsibilities inherent in each. Meanwhile, RMP in California is also seeking similarly productive arrangements with Model Cities, Office of Economic Opportunity, Migrant Health and local and county programs and activities in health.

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\*A Agency—Based on Section 314(a) which authorizes in each state a health planning agency to carry out Public Law 89-749. The A Agency in California is the State Department of Public Health. B Agency—Based on Section 314(b) which decrees establishment of area-wide health planning agencies. There are nine authorized B agencies in California.

## Information

### Current Concepts of Calcium Absorption

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ALTHOUGH THE BIOLOGICAL ACTIVITY and the therapeutic usefulness of vitamin D has been recognized for almost fifty years, it is only within the last decade that the specific metabolic effects of its role in calcium absorption have been elucidated. With advanced understanding of the mechanism of action of vitamin D, and the isolation of the active metabolite of this vitamin, it has been possible to test our hypothesis of the actual mechanics of calcium absorption in the gut. The isolation of a calcium-binding protein from the intestinal mucosal cell, and the demonstration of a calcium-dependent ATPase system active in the immediate transport of calcium have all subsequently followed these initial studies.

#### Historical

Mellanby, in 1919, was one of the earliest investigators to demonstrate the relationship between rickets and vitamin D insufficiency.<sup>1</sup> Having produced rickets in dogs by maintaining weaned six-weeks-old puppies on a cereal diet in a room devoid of sunlight, he was able to reverse the symptoms of rickets by administration of cod liver oil. In 1922, McCollum named

this active substance found in cod liver oil vitamin D, and showed that it was different from the recently isolated fat soluble vitamin, vitamin A.<sup>2</sup> In 1924, Steenbock expanded the understanding of vitamin D metabolism with the discovery that ultra-violet radiation to both food and animals produced anti-rachitic activity.<sup>3</sup> Subsequent to these reports, vitamin D was isolated and was shown to be a sterol. It was chemically synthesized and since then its therapeutic usefulness has become well known.

#### Vitamin D

The initial steps in understanding calcium absorption were elucidated with the advent of radioactive vitamin D. In 1955, Kodicek, using the first radioactive-labeled vitamin D preparation (a C<sup>14</sup>-labeled ergocalciferol), studied vitamin D absorption.<sup>4</sup> He found the administered radioactivity was primarily localized to the blood, liver and kidneys. In 1963, <sup>3</sup>H-vitamin D was prepared by Norman and DeLuca.<sup>5</sup> A similar compound was prepared by Thompson and associates and used in humans to measure absorption of vitamin D.<sup>6</sup> These investigators showed that the vitamin was fat-soluble, was taken up by the intestinal lymphatic chain and was primarily absorbed in the ileum. DeLuca corroborated these findings, showing 45 to 100 percent of the radioactivity of the plasma localized to the chylomicron lipoprotein fraction after absorption from the intestine.<sup>5</sup>

In 1967, Avioli and his group further demonstrated the intestinal absorption of the vitamin via the lymphatics.<sup>7</sup> In their studies with thoracic duct cannulation in normal patients, radioactivity appeared in the lymph quite early after oral ingestion of radioactive vitamin D<sub>3</sub>. They also reported on patients with bowel fistulas and common bile duct obstruction, and showed that vitamin D was not absorbed in the absence of bile salts. Similar presumptive evidence for the obligatory role of bile salts in vitamin D absorption had been shown by DeLuca et al<sup>5</sup> and by Thompson and co-workers.<sup>6</sup>

#### Active Metabolite 25-Hydroxycholecalciferol

From the preceding studies, we see that the initial step in understanding calcium absorption was elucidated with the advent of radioactive

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vitamin D. Vitamin D was shown to be absorbed from the gastrointestinal tract via the lymphatics and from there transported to the liver in the chylomicron fraction of the plasma. DeLuca et al, in 1966, showed that vitamin D was hydroxylated in the liver to an active metabolite, 25-hydroxycholecalciferol (25-HCC).<sup>8</sup> In his studies he showed that after administration of radioactive vitamin D<sub>3</sub>, the radioactivity was localized in the chylomicron lipoprotein fraction of the plasma. He separated this radioactivity into five bands, four of which were lipoproteins and the fifth an alpha-2 globulin. Purification of this alpha-2 globulin band recovered essentially all the active metabolic form of the vitamin D. This fraction proved to be one and a half to two times biologically more active in restoring normal calcium balance in vitamin D-deprived animals and was equally effective in mobilizing calcium from the bone of animals that had been kept on low calcium diet. Chemical isolation showed this band to be 25-hydroxycholecalciferol (25-HCC). From previous studies it had been known that there was an 8- to 10-hour delay to stimulate calcium transport in rachitic animals when vitamin D was given alone. With 25-HCC, the onset of action was only three hours.

To reiterate, following absorption from the gut, vitamin D is transported to the liver, where it is hydroxylated to 25-HCC, the active metabolic form. From the liver, 25-HCC is transported bound to an alpha-2 globulin. After 8 to 10 hours, much of the radioactivity of the labeled vitamin D is found within the mucosal cell nuclei of the small intestine. It is presumed that the bound 25-HCC is attached to the nuclear membrane of the mucosal cell. As was previously said, the "lag" which exists following the administration of vitamin D to rachitic animals, for the enhanced calcium absorption, is only partially accounted for by the formation of 25-HCC. This implies that there are additional steps which occur between the interaction of vitamin D and the subsequent enhanced calcium absorption.

### Calcium-Binding Protein

Wasserman and Taylor, in 1966, isolated a protein which was produced in the intestinal mucosa of animals who had been stimulated by

vitamin D after having been reared on a vitamin D-deprived diet.<sup>9</sup> This protein had specific calcium-binding properties and was present in low levels in the rachitic animals. When vitamin D was given to these animals, the protein was increased several fold. This protein, labeled calcium-binding protein (CaBP), was isolated from the kidneys, liver and muscle in addition to the mucosa of the duodenum, jejunum, ileum and colon. Of interest was the finding that vitamin D stimulation of the mucosa of rachitic animals produced elevated levels of CaBP only in those areas of the gastrointestinal tract where calcium was absorbed, the duodenum, jejunum and ileum. The conclusions of Wasserman and Taylor were that the calcium-binding protein was produced in the intestinal mucosa following stimulation by vitamin D, and this protein facilitated the movement of calcium across the intestinal mucosa. They isolated the protein and found that it consisted of not one but actually several closely associated proteins capable of binding calcium. To prove the association between the calcium-binding protein and the absorption of calcium, they made the following observations:

- The calcium-binding protein which was present in very low levels increased in the rachitic intestinal mucosa about the same time as the demonstrated increase in calcium absorption occurred following vitamin D administration.
- In vitamin D deprived chicks, the lowered level of CaBP and the decrease of calcium absorption were of the same order of magnitude.
- Mucosal CaBP concentration varied as the calcium absorption efficiency of the gastrointestinal tract varied—that is greater in the duodenum than in the jejunum and greater in the jejunum than the ileum.
- Younger chicks, those with a higher growth rate and more need for calcium, had more mucosal CaBP than older or more mature chickens which had completed growth.
- Laying hens or pregnant rats had more CaBP in their intestinal mucosa than non-laying chicks or non-pregnant rats. (This effect was not reduplicated by estrogen replacement.)
- Low calcium diet which stimulated an increase in calcium absorption, normally also produced an increase in CaBP in chickens.

- In chickens, where vitamin D<sub>3</sub> has a greater physiological effect than vitamin D<sub>2</sub>, there was a higher mucosal content of cAMP following administration of vitamin D<sub>3</sub> than vitamin D<sub>2</sub>.

## Calcium-Dependent ATPase System

The time between vitamin D replacement in rachitic animals and the enhanced calcium absorption still is not completely accounted for by the hydroxylation of vitamin D to form 25-HCC or by the formation of cAMP. The final step was proposed by Martin and DeLuca in 1969 when they demonstrated that immediate calcium uptake across the brush border of the intestinal mucosal cell was oxygen-dependent, required active transport, and included a calcium-dependent ATPase system.<sup>10</sup> This ATPase has been shown to be induced by vitamin D and its active metabolite 25-HCC, and is located at the site of calcium absorption—that is, the brush border of the intestinal mucosal cell. It has been shown to be present in low amounts or absent in vitamin D-deprived animals and it increases synchronously with the appearance of vitamin D-induced calcium transport in these animals. Magnesium, which has recently been shown to be important in calcium transport, is required for the ATPase system. DeLuca and his co-workers concluded that both the cAMP and the calcium-dependent ATPase systems were the proteins induced by vitamin D replacement and were responsible for calcium transport. They expressed belief that the cAMP is playing its major role in transcellular calcium movement and absorption regulation in calcium deficiency states, while the calcium-dependent ATPase system plays its role in the immediate absorption of calcium across the intestinal brush border.

## Summation of the Physiology of Absorption

What is known thus far of the physiology of calcium absorption may be summarized briefly by stating that calcium absorption occurs with the oral ingestion of the fat soluble vitamin D which is absorbed across the intestinal mucosa into the lymphatics. It is carried in the chylomicron portion of the plasma to the liver, where it is hydroxylated to the active form (25-HCC) and then transported via an alpha-2 globulin to the nuclear membrane of the intestinal mucosal cell. At this

site it may act on messenger RNA-DNA synthesis of two proteins—one of them the calcium-binding protein (cAMP) which is thought to be responsible for the transcellular calcium transport and the facultative absorption regulation of calcium, and the other the calcium-dependent ATPase protein which may be responsible for the immediate absorption of calcium across the intestinal brush border. The requirements for calcium absorption may then be listed as: (1) an intact absorptive surface, (2) the presence of vitamin D, (3) the ability to convert vitamin D to its active metabolite 25-HCC, (4) the presence of cAMP, and finally (5) the calcium-dependent ATPase system.

## Clinical Applications

Clinical malabsorption of calcium may occur because of an interruption of the intestinal absorptive surface, or the inability of the liver to form the active metabolite of vitamin D, or through failure of the absorption of the fat-soluble vitamin D itself. The malabsorptive states, including adult celiac disease, diffuse inflammatory processes such as regional enteritis, and the infiltrative processes such as lymphoma or Whipple's disease, are clinical examples of interruption of the intestinal absorptive surface. Primary malabsorption may also be the result of bacterial overgrowth, as in the "blind loop" syndrome, or following surgical removal as in the postgastrectomy states. Steatorrhea with primary failure of absorption of the fat-soluble vitamin D occurs from a variety of causes, such as those described above or from failure of pancreatic or biliary function.

In a study attempting to discern the relative importance of vitamin D absorption and calcium absorption, Thompson et al (1966) studied 12 patients with adult celiac disease or pancreatic or biliary insufficiency.<sup>6</sup> In one group there were five patients with adult celiac disease, representing malabsorption, and a second group of seven patients with pancreatic or biliary insufficiency representing maldigestion. In each group, vitamin D absorption was studied and all patients were found to malabsorb vitamin D. It was only in the first group, the patients with adult celiac disease, that decreased calcium absorption was demonstrated. These investigators concluded that the primary role of vitamin D deficiency on calcium malabsorption was to affect intestinal mu-



cosal protein synthesis—that is calcium-binding protein synthesis. This effect was more pronounced in patients with intestinal mucosal abnormalities than in those with pancreatic or biliary maldigestion. A similar study was done by Sjöberg and Nilsson (1970).<sup>11</sup> They studied 11 patients with regional enteritis and 12 patients with pancreatic insufficiency and found that calcium absorption was significantly less in patients with reduced intestinal absorptive surface (regional enteritis) than in the maldigestion produced by pancreatic insufficiency.

The studies demonstrating significant calcium malabsorption with adult celiac disease or regional enteritis as compared with pancreatic insufficiency should not imply that vitamin D deficiency is not a significant cause of calcium malabsorption. It is well known that hypocalcemia may be induced by primary vitamin D deficiency. In clinical practice today in most parts of the world, vitamin D deficiency is generally secondary to malabsorption associated with tropical or nontropical sprue. Malabsorption of calcium may also be a feature of "vitamin D-resistant" rickets, osteomalacia, parathyroid insufficiency, hyperadrenalcorticism, or hyperthyroidism. Pharmacological malabsorption of calcium may be produced chemically, by ingestion of calcium chelating agents such as sodium phytate, sodium phosphate or EDTA (ethylenediaminetetra acetic acid). There are probably other dietary or chemical factors thus far not described which may influence the absorption of dietary calcium.

Recently, Avioli et al (1969) in studying patients with chronic renal disease found that most of the patients normally absorbed vitamin D, but there was a significant decrease in the biologically active form of vitamin D-25-hydroxycholecalciferol.<sup>12</sup> They thought this decrease in 25-HCC to be responsible for the defective intestinal absorption of calcium. Interestingly, this malabsorption of calcium is not reversed by hemodialysis, but is corrected by renal allograft or homotransplant. When they studied the concentration of calcium-binding protein activity in the duodenal mucosa in uremic rats, they found that the activity of the protein was significantly decreased. Treating the animals with the active metabolite (25-hydroxycholecalciferol) brought about an increase in intestinal transport of calcium and an increase in the calcium-binding protein activity in the intestinal mucosa. The effect of renal insufficiency

on gastrointestinal transport of calcium was also studied *in vitro* by Baerg et al (1970),<sup>13</sup> and in experimental animals by Kessner and Epstein in 1965.<sup>14</sup> Calcium malabsorption in humans with chronic renal failure was demonstrated by Messner et al.<sup>15</sup> These investigators showed that despite hemodialysis and parenteral vitamin D, calcium malabsorption persisted and could only be corrected by renal homotransplant or extremely high doses of vitamin D.

Kehayoglou et al (1968) studied the intestinal absorption of calcium in cirrhotic rats.<sup>16</sup> They found that in rats with chronic cirrhosis or in animals that had chronic ligation of the common bile duct, there was a significant decrease in calcium absorption. During the same period, Avioli and his group, in studying four patients with cirrhosis, found a slow disappearance of vitamin D from the plasma and a decreased rate of intestinal absorption of calcium.<sup>7</sup> Metabolic studies utilizing <sup>3</sup>H-D<sub>3</sub> showed not only slow disappearance of this vitamin from plasma but also a decrease in the quantity of vitamin D metabolites recovered from the urine. The speculation was that the biological transformation of vitamin D<sub>3</sub> to its active metabolite (25-HCC) in the liver was impaired and the lack of this substance contributed to the calcium malabsorption. It remains only for a study to show that giving 25-hydroxycholecalciferol to cirrhotic patients results in a correction of calcium malabsorption.

The clinical disturbances of calcium absorption that are frequently seen may be summarized as follows: Malabsorption of calcium is seen in (1) vitamin D deficiency states as well as in conditions of (2) malabsorption of the vitamin. Calcium is also malabsorbed where there is (3) significant loss of intestinal mucosa as in adult celiac disease or regional enteritis. The metabolic states of (4) parathyroid insufficiency, (5) hyperadrenalcorticism and (6) hyperthyroidism may be associated with calcium malabsorption. Calcium malabsorption may result from (7) the ingestion of pharmacological agents which bind calcium and remove it from dietary absorption. Malabsorption has been demonstrated in (8) in patients with chronic renal disease and (9) in patients with liver cirrhosis.

Understanding the basic physiology and biochemical requirements for the intestinal absorption of calcium will enable the clinician to more

fully utilize his clinical laboratory for demonstration of calcium malabsorption and his clinical applications will permit treatment of the disorder where possible.

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# Medical Education and the Family Physician

LYNN P. CARMICHAEL, M.D., *Miami*

■ *The family health care specialist is a physician who through continuity of care has developed a tenured relationship with the family. He accepts the family as the unit of care and actively promotes its health. In the past one could become a family physician through experience gained in the general practice of medicine or pediatrics. While many practitioners, internists and pediatricians have become good family doctors, none have been specifically trained for this role.*

*It is the responsibility of the family physician to provide continuing and comprehensive family health care. Health concern can be divided into demands for which the patient seeks care and needs of which the individual or family is largely unaware. The degree of "comprehensiveness" is the extent to which the needs as well as the demand are met. The role of the family physician is to be a specialist in family health care and a generalist in the provision of primary medical care.*

WHEN A NEUROSURGEON completes his training at the medical center and enters practice, medical educators and administrators have an understanding of his capabilities and his limitations—what he knows and what he can do. The same is true of gynecologists, dermatologists and all other specialists except the family physician. The reason

for this is all too evident. The medical center has never tried to train physicians as specialists in family health care nor is it able to do so as most medical schools and teaching hospitals are now structured.

It is true the medical center has supplied doctors for primary medical care but they have either been untrained such as the general practitioner or well trained but in the wrong things—for example, the internist and pediatrician. While many general practitioners, pediatricians and internists have become good family doctors, none have been prepared specifically for this role.

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The author is Director, Division of Family Medicine, University of Miami School of Medicine, Miami.

Guest Speaker's Address: Presented as part of a Panel Discussion on What Is Family Practice? at the First General Meeting at the 99th Annual Session of the California Medical Association, San Francisco, March 7 to 11, 1970.

Reprint requests to: Director, Division of Family Medicine, University of Miami School of Medicine, P.O. Box 875, Biscayne Annex, Miami, Fla. 33152 (Dr. L. P. Carmichael).

## What Makes a Family Physician?

In the past one could become a family physician through experience gained in the general practice of medicine or pediatrics. This was a slow process and even when complete was often painful and disappointing to the families who were the teaching material during this unsupervised apprentice period.

From personal experience I believe we can identify four steps in the transformation of the primary care physician into the specialist in family health care. In my case, it was the metamorphosis of a general practitioner into a family physician.

### Step 1—

In the medical center a physician-in-training rarely sees the same patient twice in the outpatient clinics. As a consequence he relates to the particular disease category such as epilepsy, hypertension or cystic fibrosis clinic. In community practice, since the location of the physician's office tends to remain stable and most patients live nearby, the same individual returns to him with different complaints and illnesses; this month for a urinary tract infection, next month for a laceration and later for a periodic health evaluation. This, then, is the first part of the process—the inauguration of a continuing relationship with the people for whom the physician cares.

### Step 2—

The model for the doctor's office when he first enters practice is the emergency room and outpatient department. This is reflected in the design of his office and in the supplies and equipment he purchases. I recently moved from the office in which I practiced for over ten years. In deciding what to discard I came across unopened medication and instruments that I felt were essential when I started practice, but had never used. My model for equipping my office had been the emergency room of the hospital.

The design of my office, too, mimicked the hospital clinic and I provided seating only for the patient and myself. I soon found the "exam room" was used more for talking than examining, and that seating provisions were inadequate. Rarely did the patient come to the office unaccompanied and his family members persisted in

crowding into the examination room no matter how severely I admonished my office help.

I had been conditioned during and after medical school to treat the family as an annoyance to be avoided except when I wished to have an autopsy permit signed. I felt the presence of the family would compromise my effectiveness and interfere with the diagnostic and therapeutic process. After several frustrating years I realized that proper management of the patient's problem required the involvement and participation of the family.

That the family is the unit of care should not surprise us. We speak of family income, family cars and family rooms. It is as families that we provide for our housing and our nutritional, recreational and spiritual needs. The family is more than a collection of individuals; it has an identity of its own. It is the unit of living.<sup>1</sup> It follows that the family is the unit of care in medical matters. This realization is the second step in the transformation.

### Step 3—

Fee-for-service is the accepted method of paying for medical care in this country. At the time of the initial contact between the doctor and patient a contract is established whereby the physician agrees to try to help the patient with his problem in exchange for a fee. The contract is legally binding on both parties and the patient may sue the doctor if he is negligent, or the doctor can file suit to collect his fee. The contract has to do with the particular episode of illness and does not imply a continued obligation.

As the community-based physician comes to know the families that he serves, there occurs a shift in the doctor-family relationship from the episodic fee-for-service approach to an on-going responsibility on the part of both physician and family. The doctor agrees to be accessible and available for whatever medical reason may occur. This is why the physician goes out at 2 o'clock in the morning to see a sick child; the fifteen or twenty dollar fee is not much of a factor. The family expresses the possessiveness of a new relationship when they speak of *our* family doctor. No wonder that he collects 95 to 98 percent of his charges.

Magraw speaks of this as "medical trusteeship."<sup>2</sup> A similar relationship is found in uni-



versities with the tenure system. The change in emphasis from fee-for-service to the establishment of a tenured relationship with the family is the next to last episode.

#### Step 4—

The final event is the result of the previous three. The practitioner finds, as Peabody suggested, that in caring for the patient the doctor comes to *care* for the patient and his family.<sup>3</sup> He becomes increasingly interested in preserving the health of his families and is disappointed when they become sick. He comes to view the seriously ill patient not as an intellectual challenge or fascinating medical detective exercise but as a friend who needs help, guidance and support. In this way the consultation and referral process becomes not an admission of incompetence nor rejection of the patient, but just one part of the total management of the patient's and the family's problem.

Because of the emphasis on health maintenance the family physician uses the illness visit as an opportunity to practice preventive medicine. The woman seen with an abscess, and treated for it, also will receive indicated procedures such as cervical cytology and tetanus immunization. The older individual with a chronic disease will be checked yearly for glaucoma or tested for tuberculosis on one of his *regular* visits. Caring for a child's respiratory infection provides the chance to inquire into family functioning.

#### What Is a Family Physician, and What Does He Do?

The metamorphosis of the G.P. is now complete. Four steps are identified: (1) the establishment of continuity with an individual, (2) seeing the family as the unit of care, (3) assumption of on-going responsibility for its health, (4) emphasis on prevention, early detection of physical and emotional disease. This, then, is my definition of the family physician: He is the doctor of medicine who assumes responsibility for the continuing health maintenance of the family.

The family physician is active in two broad areas: primary medical care and comprehensive family health care. Because he is the doctor on the spot, he must meet the medical demands

of the community he serves. He is prepared to care for the common, but not necessarily minor, medical problems brought to him. Exactly what these are depends on the nature of the community and its resources. In this role he retains much of the generalist function.

It is in comprehensive health care that the family physician is a specialist. As such he needs deep knowledge of the behavioral sciences, and his basic skills are in the affective area. Through his use of the doctor-patient relationship he is able to move his patients toward health, and with his knowledge of human behavior he becomes the leader of the health team.

His contribution to the family and society has less to do with death and disease and is more concerned with improving the quality of life.

Comprehensive care requires the team approach, with the family physician, the family health nurse and the social worker composing the primary health team. However, until we provide organized ambulatory care facilities in which the team can work, we will fall short of our goal. Another requisite is a change in the method of paying for health services from the fee-for-service approach to a full prepayment system.

Some have suggested that the role as I have described it would not satisfy the physician's need for intellectual stimulation and that the clinician requires the challenge of diagnosis and treating disease. What is satisfying implies a value judgment. The particular intellectual expertise of the family physician will be in the solving of medical care problems for the family and community. In a sense he will be a trouble shooter in delivery of care. As a front-line epidemiologist his research field will be in health services and organization.

#### What's Wrong?

The failure of medical education to develop suitable training programs for family physicians is due to many factors but it would seem that most undergraduate programs are not relevant to medical practice. It appears that most medical schools attempt to prepare their students for careers as researchers, academicians and hospital based specialists. This in the face of the fact that no single school has more than 13 percent of its graduates on medical school faculties, and

no school has less than 74 percent of its graduates in clinical practice.<sup>4</sup>

Increasing attention has been given to the process of medical education. A recent paper points out that medical school has become, paradoxically, less a preparation for becoming a practitioner and more a preparation for being a medical student.<sup>5</sup> Jason has accused the medical schools of educational malpractice and has stressed the point that if a student is to become a skilled practitioner he needs regular exposure to skilled practitioners of the type of medicine he will practice.<sup>6</sup>

## A Proposal

The spectacular advances in medical care have been, for the most part, at the secondary (hospital) or tertiary (medical center) levels of health care. Developments at the primary care level have been much slower and there has been, in fact, an alarming decrease in the number of physicians in general medical practice. Also lacking in community-based practice is an organized system of delivering comprehensive health services. Such approaches must develop if we are to provide such care on a large scale to all segments of our society.

For physicians to accept organized community-based practice as they do hospital practice, they must be exposed to models of primary care during their formative period in medical school and graduate training. Medical schools and teaching centers should develop such models separate and distinct from the hospital. This ambulatory care facility should allow the following characteristics:

1. Continuity of medical care.
2. Family orientation.
3. Accessibility and availability.
4. Health maintenance and disease prevention through  
health education,  
specific prevention,  
prompt diagnosis and treatment,  
limitation of disability  
and rehabilitation.

5. A spectrum of socio-economic groups, including the poor.
6. A prepayment system.
7. Relationship to other community organizations and resources.

The academic program in such an institution would include the following:

1. The teaching of family, community and social medicine to undergraduate students in health professions, medicine, nursing, social work, dentistry, pharmacy and the like.
2. A graduate training in primary and comprehensive care and licensure by appropriate mechanism such as the American Board of Family Practice.
3. Efforts to shorten the period of training.
4. A program of continuing education for established community based professions.
5. Opportunities for research in the delivery of health services, the educational process and epidemiology.
6. Organizational status and institutional commitment equal to the other major departments.

## Conclusion

Major changes in the medical education establishment as well as in the system of medical care must occur if we are to reach our potential in community-based health care. An argument is presented for the medical schools to establish organized ambulatory care facilities. The availability of federal funds for this purpose would provide the necessary incentive to schools of health professions.

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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BENNETT, RALPH LYNN, Inglewood. Died January 1, 1971 in Inglewood of myocardial infarction, aged 57. Graduate of University of Southern California School of Medicine, Los Angeles, 1948. Licensed in California in 1949. Doctor Bennett was a member of the Los Angeles County Medical Association.

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CHAFFEE, BURNS STODDARD, Long Beach. Died December 16, 1970 in Long Beach of cancer of the prostate, aged 90. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1912. Licensed in California in 1919. Doctor Chaffee was a member of the Los Angeles County Medical Association.

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CHANEY, ONLY JARED, Inglewood. Died November 4, 1970 in Inglewood of arteriosclerotic heart disease, aged 84. Graduate of University of Cincinnati College of Medicine, 1911. Licensed in California in 1916. Doctor Chaney was a member of the Los Angeles County Medical Association.

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GOSSARD, JESSE EARL, Altadena. Died January 8, 1971 in Altadena, aged 90. Graduate of Northwestern University Medical School, Chicago, 1907. Licensed in California in 1930. Doctor Gossard was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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HARRINGTON, ETHEL REGAN, Los Angeles. Died December 3, 1970 in Los Angeles of carcinoma of the lung and rectum, aged 78. Graduate of Rush Medical College, Chicago, 1917. Licensed in California in 1929. Doctor Harrington was a member of the Los Angeles County Medical Association.

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JACOBSON, JERRY KENNETH, San Francisco. Died December 31, 1970, aged 49, near Half Moon Bay when the plane he was piloting crashed. Graduate of University of

Michigan Medical School, Ann Arbor, 1951. Licensed in California in 1953. Doctor Jacobson was a member of the San Francisco Medical Society.

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JONES, JAMES LEWIS, Los Angeles. Died January 4, 1971 in Los Angeles of heart disease, aged 44. Graduate of Howard University School of Medicine, Washington, D.C., 1958. Licensed in California in 1959. Doctor Jones was a member of the Los Angeles County Medical Association.

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KENNEDY, BAYLES R., Oakland. Died January 23, 1971 in Oakland of heart disease, aged 55. Graduate of Columbia University College of Physicians and Surgeons, New York, 1942. Licensed in California in 1943. Doctor Kennedy was an associate member of the Alameda-Contra Costa Medical Association.

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KENNEDY, KARL ELIOT, Oakland. Died January 11, 1971 in Oakland of cancer of the lung, aged 70. Graduate of University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Kennedy was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, an associate member of the American Medical Association.

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LEITCH, EUNICE MARY AMELIA, Santa Monica. Died December 3, 1970 in Los Angeles of lung cancer, aged 56. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1940. Licensed in California in 1952. Doctor Leitch was a member of the Los Angeles County Medical Association.

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NIEBERGALL, HERBERT ARTHUR, Vista. Died December 10, 1970 in Oceanside of cancer of the bladder, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Doctor Niebergall was a member of the Los Angeles County Medical Association.

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REIDENBACH, JOHN CLARENCE, San Leandro. Died December 16, 1970 in Alameda of heart disease, aged 50. Graduate of University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1945. Doctor Reidenbach was an associate member of the Alameda-Contra Costa Medical Association.

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SHEEHAN, WILLIAM J., Santa Barbara. Died December 30, 1970 in Santa Barbara, aged 74. Graduate of Yale University School of Medicine, New Haven, 1923. Li-

censed in California in 1944. Doctor Sheehan was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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STANLEY, LEON C., Saugus. Died October 26, 1970 in Saugus, aged 59. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1946. Licensed in California in 1946. M.D. degree from California College of Medicine, 1962. Doctor Stanley was a member of the 41st Medical Society.

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TEETER, ARTHUR LEWIS, Oakland. Died December 31, 1970 in Oakland of arteriosclerotic heart disease, aged 85. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1919. Licensed in California in 1919. Doctor Teeter was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

VECKI, MORRELL E., San Francisco. Died January 16, 1971 in San Francisco, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Doctor Vecki was a member of the San Francisco Medical Society.

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WHEATLEY, WILLIAM GORDON, Woodland. Died December 13, 1970 in Woodland of heart arrest (Parkinson's disease and diabetes), aged 84. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1921. Licensed in California in 1921. Doctor Wheatley was a member of the Los Angeles County Medical Association.

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WIEAND, WARREN GEORGE, San Diego. Died January 16, 1971 in San Diego, aged 66. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1929. Licensed in California in 1947. Doctor Wieand was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

## THE CHEMISTRY OF QUALITY

High quality medical care is the end product of the interaction of two sciences: the biologic sciences—medical knowledge—and the social sciences—the application of this knowledge to the delivery of patient care.

Each scientific area requires a sound data base updated by continuing education and training in the sequential logic of problem solving: the biologic sciences to advance medical knowledge; the social sciences to assure the delivery of efficient and economical quality care. Equal parts of each science must be infused into the chemical reaction to achieve the desired result. Each also must be added in "pure" form since inadequate or inaccurate biologic or sociologic knowledge would result in an incomplete—or poor—production of quality. To assure and improve the "purity" of the ingredients and to guarantee the end result, Peer Review has been developed as the assay mechanism.

Unfortunately, however, the equation is not a simple interaction of two sciences. A host of "enzymes" operating externally to this chemical reaction can be identified which may alter the quality product. For example the rising demand for services, the medical manpower shortage, and skyrocketing costs set the end product by stressing quantity not quality. Similarly, new legislation, modern technology, broader financing, and legal factors can significantly affect the chemistry. Furthermore, beyond the reaction itself, the "consumer" of the product—the patient—may accept, reject, or modify the ultimate effect of the care by his action.

Thus the chemistry of quality is complex and interrelated to a variety of factors.

JOSEPH T. PAINTER, M.D., *President*  
*American Society of Internal Medicine*  
—Reprinted from *THE INTERNIST*, November 1970



# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## California's Retail Food Inspection Program

A REDWOOD CITY MUNICIPAL COURT recently fined a local supermarket \$3,125 for offering adulterated food for sale and maintaining unsanitary premises. This was the first court action in San Mateo County's six-month-old consumer retail food protection program, an example of a cooperative state-local retail food inspection program in which the state delegates enforcement authority to local health departments. The San Mateo County Department of Health and Welfare and the State Department of Public Health's Bureau of Food and Drug jointly developed the evidence leading to the court action.

The State Bureau of Food and Drug has 26 field inspectors working out of seven district offices to protect California consumers. The bureau enforces 13 laws regulating the manufacture, storage and sale of foods, drugs, cosmetics, and hazardous household substances. The food protection program has as its objective consumer protection from the purchase of adulterated, misbranded or falsely advertised foods from more than 30,000 California retail establishments.

In 1966 the bureau developed a retail food program to utilize the available manpower of local health departments to enforce provisions of the California Pure Foods Act in retail food establishments. In 1967, with the support of the California Conference of Local Health Officers, the California Pure Foods Act was amended to permit a local health department to request authorization from the State Department of Public Health to establish a local retail food inspection and enforcement program. This provision was carried over in the Sherman Food, Drug and Cosmetic Law which became effective November 23, 1970.

The state-local program establishes conditions under which the local health department enforces both the state law and local ordinances in

retail food establishments. After a preliminary survey by the state, the local health department makes a formal request to the State Department of Public Health for the legal authorization. The Bureau of Food and Drug trains supervisory and staff sanitarians who will be carrying out enforcement activities. The local health department is required to have a laboratory and the personnel must demonstrate the requisite skills for examining foods. After two years of operation, the State Department of Public Health evaluates the certified program.

To date five local departments have been certified: Fresno County in 1967, Long Beach City and Kern County in 1969, San Mateo and Orange counties in 1970. By a 1932 charter agreement, Los Angeles County was authorized to enforce all state food and drug laws at the local level. Sanitarians in these health departments now protect about half the California population. We anticipate that eventually local enforcement will take over this responsibility for 90 percent of the population.

Giving pure food enforcement responsibility in retail food establishments to local health departments prevents duplication of effort by state and local inspectors. Moreover, it expands the authority of local health jurisdictions. In the past, when consumers filed complaints concerning violations in their local markets, the local health department had no authority to take action and was obliged to refer the complaint to a state Food and Drug office. Local health officers support the retail food program as an asset to their consumer protection activities.

Food and drug activities are one element in the broad consumer protection program of the State Department of Public Health which is concerned with problems ranging from air and water pollution to radiation and health quackery. California is in the forefront of the nation with legislation, regulations, and industry cooperation protecting the consumer from a great variety of health hazards.



# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**SKIN SURGERY—3rd Edition**—Edited by Ervin Epstein, M.D., Associate Clinical Professor of Dermatology, University of California Medical School; Formerly Associate Clinical Professor of Medicine (Dermatology), Stanford University Medical School; Chief of Dermatology and Syphilology at Highland-Alameda County Hospital; Consultant to Oakland Area Veterans' Hospital. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1970. 647 pages, \$18.50.

Surgery of the skin has become an increasingly important part of dermatologic training and practice. This multiauthored volume is an attempt to present the most recent concepts and procedures in this rapidly expanding field. The book is directed principally toward the dermatologist but contains material of interest to all physicians concerned with skin problems of their patients.

This third edition is an extensively revised and enlarged volume compared with the preceding edition published in 1962. The number of pages and chapters has been increased almost twofold but the price of the book, unfortunately, has been increased about fivefold.

The book has 41 chapters divided into five sections. These are: General Considerations, Cold Steel Surgery, Electrosurgery, Special Procedures, and Special Locations of Diseases. The 32 contributors are either dermatologists or surgeons. The editor interprets skin surgery in the broadest sense and includes subjects ranging from traditional dermatologic procedures to diverse topics such as skin grafting, cryosurgery, chemosurgery, topical fluorouracil, immunotherapy, laser surgery, and silicone injections.

A possible criticism of the book is that some of the included techniques involve operative procedures far beyond the surgical training of most dermatologists. The editor, however, states in his introduction that special training is required for the performance of some of the procedures. The multiplicity of authors results in some repetition and lack of continuity.

The section on Special Procedures is extremely interesting but little effort is made to distinguish clearly between those procedures which are still in the realm of experimental therapy and those which are generally accepted. For example, Belisario's chapter on cytotoxic therapy of cutaneous cancer is a very controversial subject and such techniques currently have extremely limited application. Similarly the use of intralesional fluorouracil for the treatment of warts has not been proved either safe nor effective. Silicone injections, in addition, can be used only in controlled investigative studies. Comments by the editor would have helped to place some of these procedures in their proper perspective.

The editor in his own chapter does express his diminishing enthusiasm with dermabrasion for acne scars. His statement that acne surgery such as drainage of pustules increases scarring is one with which many dermatologists will disagree.

In summary this book contains much of value for the dermatologist or other physician who performs skin surgery. However, each physician must critically evaluate many of the procedures prior to their use in his practice

in terms of his own training, the most current status of the procedure, and any possible medical-legal implications.

JOSEPH W. LANDAU, M.D.

**DISADVANTAGED CHILDREN: HEALTH, NUTRITION & SCHOOL FAILURE**—Herbert G. Birch, M.D., Ph.D., and Joan Dye Gussow. Harcourt, Brace & World, Inc. and Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 322 pages, \$7.50.

In the preface, the senior author, Herbert Birch, states "we have written this book to call attention to the health problems which underlie the school failure of impoverished children. . . . What we hope for is awareness of the size and scope of the danger confronting children born of and into poverty . . . What we hope for is a program that will break the continuous intergenerational chain of poverty."

In the current climate of confrontation politics in which very often the message of social injustice and urge for reform is lost in the stridency and abrasiveness of rhetoric, this book is an outstanding exception. The pleading is most dispassionate. The text is dull reading at times. Instead of rhetoric there is an overwhelming array of facts, figures and charts. It is a reference book and it is unlikely many readers will read it cover to cover.

As a reference book it is superb. The pertinent literature is well-organized and clearly presented with sufficient detail and reproduction of the original data that one need not depend solely on the authors' inferences. There is an excellent thirty-three page reference list. There are very complete author and subject indices for easy cross-reference. He draws upon a world-wide literature and marshalls an impressive brief for his case.

The subjects that he covers in detail in relation to nutritional deficit are infant mortality and perinatal morbidity, low birth weight (prematurity) and ensuing handicaps, the bodily growth and development consequences of malnutrition, and finally the cognitive and emotional deficits due to malnourishment in mother and child. He also covers the issues of medical care for the poverty level mothers and children.

The final chapter called "Retrospect and Prospect" is an important contribution. It underscores the multifactorial nature of the health, nutrition, and learning interactions. The pitfalls of simplistic solutions of "compensatory education" and the simplistic explanations such as genetic inferiority are well-discussed. He gives an historical perspective and ends on a note of hope for meaningful amelioration based on both knowledge and a commitment to humanitarian goals.

The senior author is both a Ph.D. psychologist and a pediatrician. He is eminently qualified to select and interpret the research data. Although he has an admitted bias there is a fair and exhaustive presentation of the work in the field of malnutrition and its consequences. The book is pitched at the level of a professional audience, but I am sure that it can be read with profit by intelligent lay people. It would be well if legislators and others responsible for social planning read this work.

BEATRIX A. HAMBURG, M.D.



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# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(Formerly WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a Health Services Administration grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ALCOHOLISM AND DRUG USE

May 1-2—Drug Abuse. UCSF at Preston Hall, Presbyterian Church, Mendocino. Saturday-Sunday.

May 20—Methods of Treating Drug Abuse: Approaches for the 70's. University of California Extension, Riverside at University Commons, Riverside. Thursday. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

## CANCER

April 13—Annual Cancer Conference. San Diego County Medical Society, San Diego County Branch-American Cancer Society and US Naval Hospital, San Diego at US Naval Hospital, San Diego. Tuesday. Contact: Sidney L. Saltzstein, M.D., Dept. of Pathology, Surgical Pathology Service, University Hospital of San Diego County, 225 W. Dickinson St., San Diego 92103. (714) 291-3330.

May 17-19—Second National Conference on Breast Cancer. American Cancer Society at Century Plaza Hotel, Los Angeles. Monday-Wednesday. Newer Concepts in Management, Incidence and Mortality, High Risk Groups, The Pill, Viruses, Immunology, Cell Kinetics, Genetics, Animal Experimentation, Early Breast Cancer, Detection and Screening, Management of Primary Operable Breast Cancer, Rehabilitation. Contact: Esther Kelley, Prof. Ed. Dept., ACS, 219 E. 42nd St., New York 10017. (212) 867-3700.

June 4-5—Cancer Conference. USC. Friday-Saturday.

Continuously—Tumor Board—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 2-3 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California, San Francisco Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



## MEDICINE

- March 15-19—**Transfusion Tests and Immuno-hematology Tutorial.** American Society of Clinical Pathologists and Memorial Hospital of Long Beach at Memorial Hospital of Long Beach, Long Beach. Monday-Friday. ABO grouping, Rh testing, compatibility tests, antibody identification, hemolytic disease of the newborn, transfusion reaction investigation, quality control, records, component therapy. \$150. 40 hrs. Contact: Miss Peg Driscoll, Staff Assistant, ASCP, 710 Wolcott Ave., Chicago 60612. (212) 783-1336.
- March 17—**Fourth Annual Postgraduate Course on Respiratory Disease.** Tuberculosis and Respiratory Disease Association of Contra Costa at Holiday Inn, Concord. Wednesday. Acute and Chronic Respiratory Diseases, Effects of Inhaled Allergens in Respiratory Disease, Smoking—the Physician's Role, Lung Response to Insults and Injuries, Management of Chronic Respiratory Patient, Air Pollution Disease in our Community. \$15 6 hrs. Contact: Mitchell Tarkoff, M.D., Chmn., Medical Ed. Committee, TARDAC of Contra Costa County, 105 Astrid Dr., Pleasant Hill 94523. (415) 935-0472.
- March 19-21—**New Perspectives in Diagnosis and Management of Myocardial Infarction—1971.** American College of Cardiology and Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Friday-Sunday. Structure and Function of Heart in Acute Myocardial Infarction, Hemodynamics, New Methods for Assessment of Function and Diagnosis, Heart Block and Pacemakers, Management. \$100 members, \$125 others. 22 hrs. Contact: Miss Mary Anne McNerny, Dir., Dept. of Continuing Education Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- March 20—**Manipulative Medicine.** USC. Saturday.
- March 26-27—**Symposium: Advances in Pediatric Neurology—Annual Spring Clinic.** Sacramento Pediatric Society at Sacramento Inn, Sacramento. Friday-Saturday. Diagnosis and Management of Convulsive Disorders; Hyperkinetic Syndrome; PKU and other Metabolic Disorders; Headache Tension, Fatigue Syndrome; Neurological Exam and Diagnostic Techniques; other selected topics. Contact: P. A. Michaels, M.D., Sec., SPS, 5120 J St., Sacramento 95819. (916) 452-8144.
- March 27—**Auscultation of the Heart.** PMC. Saturday.
- April 3—**Postgraduate Symposium in Infectious Diseases.** STAN. Saturday. Recent developments in pathogenesis, diagnosis and management of patients with infection.
- April 7—**Neurology for the Internist.** LLU. Wednesday. \$25. 8 hrs.
- April 17-18—**Pathophysiology of Aging.** PMC. Saturday-Sunday.
- April 19-21—**Cardiology for the Consultant.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Monday-Wednesday. Contact: Miss Mary Anne McNerny, Dir., Dept. of Continuing Education Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- April 22—**Fourteenth Annual Physicians Symposium—Workshop on Arrhythmias and Heart Failure.** Santa Clara County Heart Association at San Jose Hyatt House, San Jose. Thursday. \$20. 6 hrs. Contact: William G. Allayaud, Exec. Dir., SCCHA, 1984 The Alameda, San Jose 95126. (408) 248-1517.
- April 22-24—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.
- April 23-24—**Second Annual Cardiac Care Symposium.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday-Saturday. \$35. Contact: Miss Marilyn Woods, OCHA, 1043 Civic Center Drive West, Santa Ana 92703. (714) 547-3001.
- April 24—**Pathogenesis and Management of Fluid and Electrolyte Imbalance.** PMC. Saturday.
- April 29—**Endocrinology.** USC. Thursday.
- May 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys An-crum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- May 3-21—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three-week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.
- May 7-8—**Neuromuscular Disorders.** USC. Friday-Saturday.
- May 12-13—**Coronary Care.** USC. Wednesday-Thursday.
- May 13-16—**California Heart Association—Annual Meeting Scientific Sessions.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: Rodman Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.
- May 14-16—**Arrhythmias, Basic Concepts, Diagnosis and Treatment.** PMC and American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. \$80 members, \$125 others. 21 hrs. Contact: PMC.
- May 16—**Ventilation Perfusion and Pulmonary Disease.** USC. Sunday.
- May 16-19—**National Tuberculosis and Respiratory Disease Association.** Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: James E. Perkins, M.D., Managing Dir., NTARDA, 1740 Broadway, New York 10019. (212) 245-8000.
- May 16-19—**American Thoracic Society.** Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: Robert Weymueller, ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 20-22—**Pulmonary Thromboembolism—1971.** UCSD and American College of Chest Physicians at UCSD. Thursday-Sunday. \$100 members, \$125 others. 18 hrs. Contact: UCSD.

May 21—**Clinical Problems in Angina Pectoris.** STAN at VA Hospital, Palo Alto. Friday. Common clinical problems, historical and physical signs, interpretation of electrocardiogram, use of phonocardiogram and treadmill exercise tests, hemodynamics, coronary arteriography, evaluation of left ventricular function, variant forms of angina, atypical clinical manifestations.

May 23—**Respiratory Physiology.** PMC. Sunday.

May 26—**Los Angeles County Heart Association—Annual Meeting.** Hilton Hotel, Los Angeles. Wednesday. Contact: LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

June 1-4—**Selected Topics on the Pathophysiology of Clinical Gastroenterology.** UCSF and American College of Physicians at UCSF. Tuesday-Friday. Contact: UCSF.

June 4-5—**Vectorcardiography.** UCSF. Friday-Saturday.

June 14-July 2—**Coronary Care for Physicians Training Program.** See Medicine, May 3-21.

June 22-23—**American Diabetes Association.** Sheraton-Palace Hotel, San Francisco. Tuesday-Wednesday. Contact: H. Richard Connelley, Exec. Dir., 18 E. 48th St., New York 10017. (212) 752-8550.

June 24-26—**Endocrine Society.** Hilton Hotel, San Francisco. Thursday-Saturday. Contact: Mrs. Nona Lee Mattox, Exec. Sec., ES, 1211 N. Shartel, Oklahoma City 73103. (405) 232-8747.

July 5-16—**Coronary Care Unit Program for Physicians.** See Medicine, May 3-14.

**Continuously—Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, M.D., LLU.

**Continuously—Coronary Care.** St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

**Continuously—Neurological Sciences.** St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

**Continuously—Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

**Continuously—Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

**Continuously—Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

**Continuously—Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

**Continuously—Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSPB, 4200 California St., San Francisco 94118. (415) 387-0934.

**Continuously—Medico-Surgical Cardiovascular Seminar.** STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

**Continuously—Cardiology Conferences—CRMP Area III.** Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

#### **Grand Rounds—Medicine**

##### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

##### **Wednesdays**

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.



12:30-1:30 p.m., University Hospital, UCSD.  
12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

#### Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.  
10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.  
Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

#### Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.  
8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.  
Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.  
1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.  
1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.  
Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

### MENTAL RETARDATION

June 7-19—Mental Retardation Workshop. UCLA. Two weeks.

### OBSTETRICS AND GYNECOLOGY

March 17-19—Fetal Monitoring. USC at El Mirador Hotel, Palm Springs. Wednesday-Friday.  
March 24—Urological Disorders in Women. LLU. Wednesday. \$25. 8 hrs.  
April 3-4—Therapeutic Abortion. PMC. Saturday-Sunday.  
May 3-6—American College of Obstetricians and Gynecologists—Annual Meeting. Hilton Hotel, San Francisco. Monday-Thursday. Perinatology, Pelvic Infections, Diseases of the Vulva. Contact: Donald F. Richardson, ACOG, 79 W. Monroe St., Chicago 60603. (312) 236-6814.  
May 7—Female Urology. See Surgery, May 7.  
May 12—Problems in Reproduction. LLU. Tuesday. \$25. 8 hrs.  
May 15—Gynecological Diseases. See Radiology-Pathology, May 15.  
May 17-19—Second National Conference on Breast Cancer. See Cancer, May 17-19.  
May 21-22—Sixteenth Annual Obstetrics and Gynecology Symposium. Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

May 26-29—The High Risk Infant: Early Detection and Preventive Intervention. See Pediatrics, May 26-29.

### Grand Rounds—Obstetrics and Gynecology

#### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.  
10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.  
11:30 a.m., First Floor Auditorium, Room 13-105, UCLA Medical Center. UCLA.  
12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

#### Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

#### Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

#### Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

### PEDIATRICS

March 18-21—Association of Convalescent Homes and Hospitals for Asthmatic Children. Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: Israel Friedman, Exec. Vice Pres., ACHHAC, Lincoln Road, Miami Beach 33139. (305) 538-1187.  
March 22-25—Clinical Evaluation of Children with Learning Disorders. UCSF. Monday-Thursday. Physician's role in history, physical and neurological examination, academic achievement screening, family interview, interpretation of findings to the child and his family, working with family and school in formulating and following through on plans of management. 18½ hrs.  
March 26-27—Symposium: Advances in Pediatric Neurology—Annual Spring Clinic. See Medicine, March 26-27.  
April 23-24—Sixteenth Annual Pediatric Symposium. Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Environmental Pediatrics. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.  
April 24—Pediatric Otolaryngology. PMC. Saturday.  
May 13-15—Advances in Pediatrics. UCSF. Thursday-Saturday.  
May 15-16—Northern California Chapter, American Academy of Pediatrics—Annual Spring Meeting. Yosemite Lodge, Yosemite. Saturday-Sunday. Contact: Birt Harvey, M.D., 1101 Welch Road, Suite A-1, Palo Alto 94304.

May 26-27—**The High Risk Infant: Early Detection and Preventive Intervention.** Mt. Zion Medical Center and the National Foundation, March of Dimes at Jack Tar Hotel, San Francisco. Wednesday-Saturday. Multidisciplinary attempt to synthesize newest information concerning foetal, infant and child development in the crucial first three years of life. Genetic, cross-cultural, ecologic, nutritional, physiological, psychological and emotional aspects. Contact: Ruth Gross, M.D., Mt. Zion Medical Center, 1600 Divisadero St., San Francisco 94115. (415) 567-6600.

June 4—**Annual Premature Day.** STAN. Friday. Neonatal intensive care and highlights of research.

June 10-12—**Advances in Pediatrics.** UCSF. Wednesday-Saturday.

#### Grand Rounds—Pediatrics

##### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

##### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

##### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

##### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

#### PSYCHIATRY

April 2—**Introduction to Child Psychiatry.** Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Fridays through June 4. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

April 6.—**Schools of Psychiatric Thought.** Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Tuesdays through June 22. Contact: J. Elizabeth Jeffress, M.D., Chief, Professional Education, Agnews State Hospital, San Jose 95114. (408) 262-1200.

April 7—**Group Methods.** UCSF at V A Hospital, San Francisco. Wednesdays through June 9. \$30 full program, \$20 lectures only, \$2 individual lectures. 15 hrs.

April 27-June 29—**Psychodynamics of Behavior.** UCLA. Tuesday evenings.

May 1—**Group Process.** UCSF at Modesto State Hospital, Modesto. Saturday.

July 23-25—**Workshops in Clinical Hypnosis and Hypnotherapy.** American Society of Clinical Hypnosis at St. Francis Hotel, San Francisco. Friday-Sunday. \$125. Contact: F. D. Nowlin, Exec. Sec., ASCH, 800 Washington Ave., Minneapolis 55414. (612) 331-9452.

#### Grand Rounds—Psychiatry

##### Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

#### RADIOLOGY—PATHOLOGY

April 10—**Scintillation Camera Workshop.** UCSF. Saturday.

April 30-May 1—**Radiology of the Liver, Biliary Tract and Pancreas—Fourth Annual Leo G. Rigler Radiology Symposium.** UCLA. Friday-Saturday.

May 15—**Gynecological Diseases.** South Bay Radiology and Pathology Society at Little Village Theater, Carmel. Saturday. \$20. Contact: Robert M. Rinehart, M.D., Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262.

June 7-19—**Biological Electron Microscopy.** USC at Allan Hancock Foundation Building, USC. Two weeks. Designed for professional and laboratory personnel desiring knowledge and experience in tissue preparation for examination with electron microscope. Contact: Dr. Robert F. Bills, Dir., Electron Microscopy Laboratory, USC. (213) 746-6015.

June 21-26—**Pathology of the Lung.** UCSD. Monday-Saturday. \$200. 48 hrs.

July 10—**Scintillation Camera Workshop.** UCSF. Saturday.

Continuously—**UCSF Radiology Rounds, Seminars, and Conferences.** Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiology Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.



Continuously—Principles and Clinical Uses of Radioisotopes. UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

#### Grand Rounds—Radiology-Pathology

##### Mondays

Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

##### Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

#### SURGERY—ANESTHESIOLOGY

March 19-20—Sixteenth Annual Surgical Symposium. Southern California Permanente Medical Group at Ambassador Hotel, Los Angeles. Friday-Saturday. Diseases of the alimentary tract. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

March 24—Urological Disorders in Women. See Ob/Gyn, March 24.

April 1-2—General Surgery. UCSF. Thursday-Friday. Commonly encountered surgical problems, care of injured patients, surgical gastrointestinal diseases, important areas of surgical hemostasis and surgical infections, trauma, carcinoma of the colon, problems in diseases of the biliary tree. \$70. 12 hrs.

April 2-3—Proctology. UCSF. Friday-Saturday. Clinical demonstration of techniques, audio-visual presentations and small group discussions. \$60. 8 hrs.

April 6—Postgraduate Refresher Course in Orthopaedic Surgical Anatomy. Southern California Division, International College of Surgeons and Orthopaedic Hospital, Los Angeles at Orthopaedic Hospital, Los Angeles. Tuesday evenings through June 8. Surgical anatomy, prosections by surgical anatomist, cadaveric surgery and clinical discussions. \$120. 20 hrs. Contact: Darline Murphy, Exec. Sec., Southern Calif. Div., ICS, 136 N. Brighton, Burbank 91506. (213) 846-0669.

April 8—Surgical and Clinical Anatomy of the Vascular System. Southern California Division, International College of Surgeons and Orthopaedic Hospital, Los Angeles at Orthopaedic Hospital, Los Angeles. Thursday evenings through May 27. Prosections by surgical anatomist, cadaveric surgery and clinical discussions. \$100. 16 hrs. Contact: Darline Murphy, Exec. Sec., Southern Calif. Div., ICS, 136 N. Brighton, Burbank 91506. (213) 846-0669.

April 16-17—Vascular Surgery. USC at Hilton Hotel, Los Angeles. Friday-Saturday.

April 17-18—Sixteenth Annual Postgraduate Assembly—Los Angeles Society of Anesthesiologists. Hilton Hotel, Los Angeles. Saturday-Sunday.

April 19-21—Glaucoma Conference. UCSF at St. Francis Hotel, San Francisco. Monday-Wednesday. Current concepts in the evaluation and therapy of the glaucomas, highlighted by discussion of problem cases. Present status and future role of microsurgical approach to glaucoma control. \$100.

April 24—Pediatric Otolaryngology. See Pediatrics, April 24.

April 24—Application of Casts, Splints and Bandages. UCLA. Saturday.

May 1—Orthopedic Problems. UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

May 2-7—Biennial Western Conference on Anesthesiology. Princess Kaiulani Hotel, Honolulu. Sunday-Friday. \$100. Contact: Eldon E. Smith, M.D., 2270 Kalahua Ave., Suite 1708, Honolulu 96814.

May 7—Female Urology. USC at Biltmore Hotel, Santa Barbara. Friday.

May 8—Audiology. PMC. Saturday.

May 23-24—American Laryngological Association. Hilton Hotel, San Francisco. Sunday-Monday. Contact: Frank D. Lathrop, M.D., R.D. #1, Pittsford, Vermont 05763. (802) 483-6430.

May 25-26—American Broncho-Esophagological Association. Hilton Hotel, San Francisco. Tuesday-Wednesday. Contact: Walter Maloney, M.D., Sec., ABEA, 2065 Adelbert Rd., Cleveland 44106. (216) 791-7300.

May 25-27—American Laryngological, Rhinological, and Otological Society. Hilton Hotel, San Francisco. Tuesday-Thursday. Contact: Louis E. Silcox, M.D., 108-11 Lankenau Medical Bldg., Philadelphia 19151. (215) 642-0136.

May 25-27—American Academy of Facial Plastic and Reconstructive Surgery. Hilton Hotel, San Francisco. Tuesday-Thursday. Contact: Carl N. Patterson, M.D., Sec., 1110 W. Main St., Durham, North Carolina 27701. (919) 682-9341.

May 28-29—American Otological Society. Hilton Hotel, San Francisco. Friday-Saturday. Contact: Wesley H. Bradley, M.D., 1100 E. Genesee St., Syracuse, New York 13210. (315) 476-3124.

June 3-4—Highlights of Modern Ophthalmology. PMC. Thursday-Friday.

June 12—Orthopedics. PMC. Saturday.

June 24-26—1971 Stanford Ophthalmology Conference. STAN. Thursday-Saturday. Present state of knowledge in fields of ocular motility and ptosis, strabismus.

July 6—Annual Basic Science Course in Ophthalmology. STAN. Eight and one-half weeks through September 3. Designed primarily for residents. Instruction, lectures and laboratory sessions, emphasis on application of basic science principles to clinical situations and disease conditions.

July 26-28—The Shoulder in Sports. American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. 24 hrs. Contact: Fred Behling, M.D., 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

## Grand Rounds—Surgery

### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

### Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

### Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. USCD.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

## OF INTEREST TO ALL PHYSICIANS

March 18-21—Association for the Advancement of Medical Instrumentation. International Hotel, Los Angeles. Thursday-Sunday. Contact: Michael J. Miller, AAMI, 9650 Rockville Pike, Bethesda, Md. 20014.

April 12—Medical Centers of the Orient. USC on tour in Japan, Taiwan, Thailand, Singapore, Malaysia and Hong Kong. One month through May 12.

April 17-18—Kern Postgraduate Conference. Kern County Medical Society at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: Milton L. Smale, M.D., Chairman, 1930 Eighteenth St., Bakersfield 93301. (805) 327-7637.

April 21-22—Eighth Annual Spring Symposium for Physicians Practicing General Medicine. Los Angeles County Heart Association and Los Angeles County Academy of General Practice at Ambassador Hotel, Los Angeles. Wednesday-Thursday. 10 hrs. Contact: Joyce Martin, Program Associate, LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

April 27-May 1—Hawaii Medical Association Annual Meeting. Ilikai Hotel, Honolulu. Tuesday-Saturday. Contact: H. Tom Thorson, Acting Exec. Dir., HIMA, 510 S. Beretania St., Honolulu 96813. (808) 536-7702.

April 28-May 1—American College Health Association. Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: James W. Dilley, Excc. Sec., ACHA, 2807 Central St., Evanston, Ill. 60201. (312) 491-9775.

May 1—Facial Pain. PMC. Saturday.

May 5-6—Intensive Care Unit: A Team Approach. PMC. Wednesday-Thursday.

May 7-8—Trauma. UCSF. Friday-Saturday.

May 8—Utilization Review in Hospitalized Patients. UCSF at St. Francis Hotel, San Francisco. Saturday.

May 8—Life or Death—The Individual's Right to Choice. UCSF. Saturday.

May 8—Second Annual Clinical Pharmacology Symposium: Current Concepts in Drug Therapy for the Practicing Physician. STAN and Palo Alto Medical Clinic at Palo Alto Medical Clinic, Palo Alto. Saturday. \$15.

### CMA Postgraduate Institutes and Circuit Courses

April 30-May 1—San Joaquin Valley Counties Regional Postgraduate Institute. CMA, UCLA and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. \$20. Contact: CMA.

May 14-15—Redwood Regional Postgraduate Institute. CMA, STAN and Humboldt-Del Norte County Medical Society at Eureka Inn, Eureka. Friday-Saturday. \$20. Contact: CMA.

June 17-18—Sacramento Valley Counties Regional Postgraduate Institute. CMA, USC and Sacramento County Medical Society at Sahara-Tahoe Hotel, Lake Tahoe. Thursday-Friday. \$20. Contact: CMA.

May 15—Third Annual Symposium—Baldwin Hills Hospital. Proud Bird Restaurant, Los Angeles. Saturday. Refresher course for general practitioner. Medical emergencies in the office; cardiac shock, hematological emergency, cardiac emergency, drug interactions, respiratory emergency. 6½ hrs. Contact: Howard R. Bierman, M.D., Program Chmn., Baldwin Hills Hospital, 5525 W. Slauson Ave., Los Angeles 90056. (213) 645-2110.

May 22—Annual Seminar—General Hospital of Ventura County. Saturday. Contact: J. Austin Daly, M.D., General Hospital of Ventura County, Ventura 93003. (805) 648-6181.

May 22—Medical Alumni Reunion Clinical Symposium. STAN. Saturday.

May 23—Examination Room Techniques: A Symposium for Medical Assistants. UCSF. Sunday.

May 27—Medical Centers of Africa. USC in Senegal, Ivory Coast, Ghana, Uganda, Kenya. Three weeks.



June 13-17—**Western Area Conference of Foundations for Medical Care.** United Foundations for Medical Care Service Corporation at Kauai Surf Hotel, Lihue, Kauai, Hawaii. Sunday-Thursday. Contact: Norman A. Brown, Exec. Sec., 1625 Franklin Ave., Santa Rosa 95404.

June 30-July 4—**Seminar for General Practitioners.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

July 16-17—**Effective Scientific Communication.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Friday-Saturday. \$225.

Continuously—**Basic Science Correlation in Disease.** VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.

Continuously—**Ventura General Hospital Program.** UCI and Ventura General Hospital at Ventura General Hospital, Ventura. Monthly lectures by UCI faculty. Contact: UCI.

Continuously—**Postgraduate Medical Lecture Series—Orange County.** UCI and Orange County Chapter, American Academy of General Practice at Saddleback Inn, Santa Ana. Monthly lectures by UCI faculty. April 12, Orthopedic Examination of Hips and Feet in Infants and Children; May 10, Manipulative Bodily Therapy; June 4, Secondary Hypertension. Contact: UCI.

Continuously—**Postgraduate Medical Lecture Series—Riverside-San Bernardino.** UCI and Riverside-San Bernardino Chapter, American Academy of General Practice at Rams Horn Inn, San Bernardino. Monthly lectures by UCI faculty. March 18, Current Concepts and Management of Hepatitis; April 15, General Plastic and Reconstructive Surgery; May 21, Diagnosis and Management of Bleeding Disorders. Contact: UCI.

Continuously—**Educational Tape Service for Orthopaedists, Rheumatologists.** Orthopaedic Audio-Synopsis Foundation. Monthly recorded teaching program on C-60 cassette tapes available to orthopaedic surgeons, rheumatologists and resident physicians. Twelve monthly tapes, annual subscription rate of \$72 (\$50 for residents). Contact J. Tonn, Managing Editor, Orthopaedic Audio-Synopsis Foundation, 6317 Wilshire Blvd., Los Angeles 90048. (213) 986-0131.

Continuously—**Inter-Hospital Conference.** UCSD and participating hospitals in the San Diego area at Radiology main conference room, UCSD. Weekly conferences conducted by various hospitals. Consult UCSD for dates and participating hospitals.

Continuously—**Weekly Seminar for Graduate Students.** UCSD at Basic Sciences Building, UCSD. Weekly Wednesday seminars, open to interested physicians. 12 noon.

Continuously—**Dean's Day Program.** UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. March 25, Radiology; April 22, Community Medicine. Contact: UCSD.

Continuously—**Biomedical Lecture Series.** UCSD. March 17, April 21, May 19, 8:00 p.m., Basic Sciences Building, UCSD.

Continuously—**Basic Science Lecture Series.** UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

Continuously—**Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malpractice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MMN Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all California medical schools. Contact: Richard R. Getz, Exec. Dir., MMN, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

Continuously—**Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Practicing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Endocrinology, Metabolism, Gastroenterology, Hematology, Neurology, Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: February-March, April-May. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, environmental radiation standards and nuclear power plants, overpopulation, abortion and contraception, technological problems of power generation in the United States, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and supersonic transport. Contact: John W. Farquhar, M.D., Assoc. Prof. of Medicine, STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(Formerly WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

**THIS BULLETIN** of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a Health Services and Mental Health Administration grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ALCOHOLISM AND DRUG USE

May 15—**Drug Abuse.** UCSF at Preston Hall, Presbyterian Church, Mendocino. Saturday.

May 20—**Methods of Treating Drug Abuse: Approaches for the 70's.** University of California Extension, Riverside at University Commons, Riverside. Thursday. Emergency and long-range treatment of drug users, methadone treatment, emergency medical treatment, community resources for treating drug abuse. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

## CANCER

May 17-19—**Second National Conference on Breast Cancer.** American Cancer Society at Century Plaza Hotel, Los Angeles. Monday-Wednesday. Newer Concepts in Management, Incidence and Mortality, High Risk Groups, The Pill, Viruses, Immunology, Cell Kinetics, Genetics, Animal Experimentation, Early Breast Cancer, Detection and Screening, Management of Primary Operable Breast Cancer, Rehabilitation. Contact: Esther Kelley, Prof. Ed. Dept., ACS, 219 E. 42nd St., New York 10017. (212) 867-3700.

June 4-5—**Cancer Conference.** USC. Friday-Saturday.

Continuously—**Tumor Board—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 2-3 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board,

Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## MEDICINE

April 16—**Symposium on Nutrition.** USC. Friday.

April 19-21—**Cardiology for the Consultant.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Monday-Wednesday. Contact: Miss Mary Anne McInerney, Dir., Dept. of Continuing Education Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California, San Francisco Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



- April 22—**Fourteenth Annual Physicians Symposium—Workshop on Arrhythmias and Heart Failure.** Santa Clara County Heart Association at San Jose Hyatt House, San Jose. Thursday. \$20. 6 hrs. Contact: William G. Allayaud, Exec. Dir., SCCHA, 1984 The Alameda, San Jose 95126. (408) 248-1517.
- April 22-23—**Hypertension.** UCSF. Thursday-Friday.
- April 23-24—**Second Annual Cardiac Care Symposium.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday-Saturday. \$35. Contact: Miss Marilyn Woods, OCHA, 1043 Civic Center Drive West, Santa Ana 92703. (714) 547-3001.
- April 24—**Pathogenesis and Management of Fluid and Electrolyte Imbalance.** PMC. Four Saturday workshops, July 24, October 23, and January 22. \$50 per session, \$150 for four sessions.
- April 29—**Endocrinology.** USC. Thursday.
- May 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- May 3-21—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three-week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.
- May 7-8—**Neuromuscular Disorders in Children and Adults.** USC. Friday-Saturday.
- May 12-13—**Coronary Care.** USC. Wednesday-Thursday.
- May 13-16—**California Heart Association—Annual Meeting Scientific Sessions.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Medical and Surgical Aspects of Coronary Artery Disease and Prosthetic Valve Replacement. \$15. Contact: Rodman Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.
- May 14-16—**Arrhythmias, Basic Concepts, Diagnosis and Treatment.** PMC and American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. \$100 members, \$145 others. 21 hrs. Contact: PMC.
- May 15—**Oral Lesions in Dermatology.** STAN. Saturday.
- May 16—**Ventilation Perfusion and Pulmonary Disease.** USC. Sunday.
- May 16-19—**National Tuberculosis and Respiratory Disease Association.** Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: James E. Perkins, M.D., Managing Dir., NTARDA, 1740 Broadway, New York 10019. (212) 245-8000.
- May 16-19—**American Thoracic Society.** Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: Robert Weymueller, ATS, 1740 Broadway, New York 10019. (212) 245-8000.
- May 19-20—**Coronary Artery Disease.** USC. Wednesday-Thursday.
- May 20-22—**Pulmonary Thromboembolism—1971.** UCSD and American College of Chest Physicians at UCSD. Thursday-Sunday. \$100 members, \$125 others. 18 hrs. Contact: UCSD.
- May 21—**Clinical Problems in Angina Pectoris.** STAN at VA Hospital, Palo Alto. Friday. Common clinical problems, historical and physical signs, interpretation of electrocardiogram, use of phonocardiogram and treadmill exercise tests, hemodynamics, coronary arteriography, evaluation of left ventricular function, variant forms of angina, atypical clinical manifestations.
- May 23—**Respiratory Physiology.** PMC. Sunday.
- May 26—**Los Angeles County Heart Association—Annual Meeting.** Hilton Hotel, Los Angeles. Wednesday. Contact: LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.
- May 27-29—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.
- June 1-4—**Selected Topics on the Pathophysiology of Clinical Gastroenterology.** UCSF and American College of Physicians at UCSF. Tuesday-Friday. Esophagus—structure, function and diseases including reflux; Stomach—evaluation of gastric secretion, diseases; Small intestine—small gut absorption and histology, diseases; Liver—evaluation of function and diseases; Colon—roentgenology and diseases; Pancreas—pancreatic secretion and diseases; Biliary tract—function of bile, gallstones. Esophagitis and stricture, peptic ulcer, malabsorption diseases, hepatic and cirrhosis, cholelithiasis, inflammatory diseases of the gut. Contact: UCSF.
- June 5—**Tuberculosis.** UCSF. Saturday.
- June 14-July 2—**Coronary Care for Physicians Training Program.** See Medicine, May 3-21.
- June 16-19—**Third Annual Cerebral Function Symposium.** Annual Cerebral Function Symposium at Hotel del Coronado, Coronado. Wednesday-Saturday. Hemispherectomy and Cerebral Function. Contact: W. Lynn Smith, Ph.D., Suite 1120, Franklin Medical Center, 2045 Franklin, Denver 80205. (303) 534-0903.
- June 18-20—**Cardiology.** UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Friday-Sunday.
- June 22-23—**American Diabetes Association.** Sheraton-Palace Hotel, San Francisco. Tuesday-Wednesday. Contact: H. Richard Connelley, Exec. Dir., 18 E. 48th St., New York 10017. (212) 752-8550.
- June 24-26—**Endocrine Society.** Hilton Hotel, San Francisco. Thursday-Saturday. Contact: Mrs. Nona Lee Mattox, Exec. Sec., ES, 1211 N. Shartel, Oklahoma City 73103. (405) 232-8747.
- July 5-16—**Coronary Care Unit Program for Physicians.** See Medicine, May 3-14.

**Continuously—Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, M.D., LLU.

**Continuously—Coronary Care.** St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

**Continuously—Neurological Sciences.** St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

**Continuously—Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

**Continuously—Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

**Continuously—Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

**Continuously—Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

**Continuously—Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSPB, 4200 California St., San Francisco 94118. (415) 387-0934.

**Continuously—Medico-Surgical Cardiovascular Seminar.** STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

**Continuously—Cardiology Conferences—CRMP Area III.** Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

## **Grand Rounds—Medicine**

### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

### **Wednesdays**

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

### **Thursdays**

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

### **Fridays**

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## **MENTAL RETARDATION**

May 23-June 4—Mental Retardation Workshop. UCLA. Two weeks.



## OBSTETRICS AND GYNECOLOGY

May 3-6—American College of Obstetricians and Gynecologists—Annual Meeting. Hilton Hotel, San Francisco. Monday-Thursday. Perinatology, Pelvic Infections, Diseases of the Vulva. Contact: Donald F. Richardson, ACOG, 79 W. Monroe St., Chicago 60603. (312) 236-6814.

May 8-9—Female Urology. See Surgery, May 8-9.

May 12—Problems in Reproduction. LLU. Tuesday. \$25. 8 hrs.

May 15—Gynecological Diseases. See Radiology-Pathology, May 15.

May 15—Conference on Estrogen Therapy and the Menopause. UCSD. Saturday.

May 17-19—Second National Conference on Breast Cancer. See Cancer, May 17-19.

May 21-22—Sixteenth Annual Obstetrics and Gynecology Symposium. Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

May 26-29—The High Risk Infant: Early Detection and Preventive Intervention. See Pediatrics, May 26-29.

### Grand Rounds—Obstetrics and Gynecology

#### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

11:30 a.m., First Floor Auditorium, Room 13-105, UCLA Medical Center. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU

#### Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

#### Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

#### Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

## PEDIATRICS

April 23-24—Sixteenth Annual Pediatric Symposium. Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Environmental Pediatrics. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

April 24—Pediatric Otolaryngology. PMC. Saturday. \$50. 8 hrs.

May 15-16—Northern California Chapter, American Academy of Pediatrics—Annual Spring Meeting. Yosemite Lodge, Yosemite. Saturday-Sunday. \$20. 8 hrs. Contact: Birt Harvey, M.D., 1101 Welch Road, Suite A-1, Palo Alto 94304.

May 26-29—Symposium on the Infant at Risk: Early Detection and Preventive Intervention. Mt. Zion Medical Center and the National Foundation, March of Dimes at Jack Tar Hotel, San Francisco. Wednesday-Saturday. Multidisciplinary attempt to synthesize newest information concerning foetal, infant and child development in the crucial first three years of life. Genetic, cross-cultural, ecologic, nutritional, physiological, psychological and emotional aspects. Contact: Ruth Gross, M.D., Mt. Zion Hospital and Medical Center, 1600 Divisadero St., San Francisco 94115. (415) 567-6600.

June 4—Annual Premature Day. STAN. Friday. Neonatal intensive care and highlights of research.

June 10-12—Advances in Pediatrics. UCSF. Wednesday-Saturday.

July 12-14—Chronic Diseases in Childhood. STAN and American Academy of Pediatrics at Childrens Hospital of Stanford, Stanford. Monday-Wednesday. Recent advances in diagnosis and treatment of chronic diseases of childhood, improved techniques for the delivery of health services to children with chronic handicapping conditions. Sections on hematology, allergy, rheumatology, clinical immunology, chest diseases, anesthesiology, psychiatry, genetics, renology, radiology, endocrinology, gastroenterology. Contact: STAN.

### Grand Rounds—Pediatrics

#### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

#### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

#### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

## Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

## PSYCHIATRY

April 27-June 29—Psychodynamics of Behavior. UCLA. Tuesday evenings.

May 1—Exploration and Process in Group Therapy. UCSF at Modesto Junior College, Modesto, Saturday.

May 8—Suicide—The Individual's Right to Choice. UCSF. Saturday.

June 28-July 2—Comparative Psychotherapies. USC Division of Postgraduate Psychiatry at Newporter Inn, Newport Beach. Monday-Friday. \$50. 15 hrs. Contact: Donald H. Naftulin, M.D., Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

July 23-25—Workshops in Clinical Hypnosis and Hypnotherapy. American Society of Clinical Hypnosis at St. Francis Hotel, San Francisco. Friday-Sunday. \$125. Contact: F. D. Nowlin, Exec. Sec., ASCH, 800 Washington Ave., Minneapolis 55414. (612) 331-9452.

## Grand Rounds—Psychiatry

### Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

## RADIOLOGY—PATHOLOGY

April 30-May 1—Radiology of the Liver, Biliary Tract and Pancreas—Fourth Annual Leo G. Rigler Radiology Symposium. UCLA. Friday-Saturday.

May 15—Gynecological Diseases. South Bay Radiology and Pathology Society at Little Village Theater, Carmel. Saturday. \$20. Contact: Robert M. Rinehart, M.D., Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262.

June 7-19—Biological Electron Microscopy. USC at Allan Hancock Foundation Building, USC. Two weeks. Designed for professional and laboratory personnel desiring knowledge and experience in tissue preparation for examination with electron microscope. Contact: Dr. Robert F. Bills, Dir., Electron Microscopy Laboratory, USC. (213) 746-6015.

June 21-26—Pathology of the Lung. UCSD. Monday-Saturday. \$200. 48 hrs.

July 10—Scintillation Camera Workshop. UCSF. Saturday.

Continuously—UCSF Radiology Rounds, Seminars, and Conferences. Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiography Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.

Continuously—Principles and Clinical Uses of Radioisotopes. UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

## Grand Rounds—Radiology-Pathology

### Mondays

Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

### Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

## SURGERY—ANESTHESIOLOGY

April 16-17—Vascular Surgery. USC at Hilton Hotel, Los Angeles. Friday-Saturday.

April 17-18—Sixteenth Annual Postgraduate Assembly—Los Angeles Society of Anesthesiologists. Hilton Hotel, Los Angeles. Saturday-Sunday. \$50.

April 17-18—Foot Deformities. UCSF. Saturday-Sunday. 9½ hrs.

April 19-21—Glaucoma Conference. UCSF at St. Francis Hotel, San Francisco. Monday-Wednesday. Current concepts in the evaluation and therapy of the glaucomas, highlighted by discussion of problem cases. Present status and future role of microsurgical approach to glaucoma control. \$100.

April 24—Pediatric Otolaryngology. See Pediatrics, April 24.

April 24—Application of Casts, Splints and Bandages. UCLA. Saturday.

May 2-7—Biennial Western Conference on Anesthesiology. Princess Kaiulani Hotel, Honolulu. Sunday-Friday. \$100. Contact: Eldon E. Smith, M.D., 2270 Kalia Ave., Suite 1708, Honolulu 96814.

May 8—Audiology. PMC. Saturday.

May 8-9—Female Urology. USC at Biltmore Hotel, Santa Barbara. Saturday-Sunday.

May 13-15—Neurosurgery. UCSF. Thursday-Saturday.

May 23-24—American Laryngological Association. Hilton Hotel, San Francisco. Sunday-Monday. Contact: Frank D. Lathrop, M.D., R.D. #1, Pittsford, Vermont 05763. (802) 483-6430.



May 23-25—American Academy of Facial Plastic and Reconstructive Surgery. Hilton Hotel, San Francisco. Sunday-Tuesday. Contact: Carl N. Patterson, M.D., Sec., 1110 W. Main St., Durham, North Carolina 27701. (919) 682-9341.

May 25-27—American Laryngological, Rhinological, and Otolological Society. Hilton Hotel, San Francisco. Tuesday-Thursday. Contact: Louis E. Silcox, M.D., 108-11 Lankenau Medical Bldg., Philadelphia 19151. (215) 642-0136.

May 26-27—American Broncho-Esophagological Association. Hilton Hotel, San Francisco. Wednesday-Thursday. Contact: Walter Maloney, M.D., Sec., ABEA, 2065 Adelbert Rd., Cleveland 44106. (216) 791-7300.

May 28-29—American Otolological Society. Hilton Hotel, San Francisco. Friday-Saturday. Contact: Wesley H. Bradley, M.D., 1100 E. Genesee St., Syracuse, New York 13210. (315) 476-3124.

June 3-4—Highlights of Modern Ophthalmology. PMC. Thursday-Friday.

June 12—Painful Feet and Injured Ankles. PMC. Saturday.

June 24-26—1971 Stanford Ophthalmology Conference. STAN. Thursday-Saturday. Present state of knowledge in fields of ocular motility and ptosis, strabismus. \$125.

July 6—Annual Basic Science Course in Ophthalmology. STAN. Eight and one-half weeks through September 3. Designed primarily for residents. Instruction, lectures and laboratory sessions, emphasis on application of basic science principles to clinical situations and disease conditions.

July 26-28—The Shoulder in Sports. American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. 24 hrs. Contact: Fred Behling, M.D., 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

#### Grand Rounds—Surgery

##### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

##### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

##### Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

##### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

#### Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

#### OF INTEREST TO ALL PHYSICIANS

April 15-16—Understanding and Interpreting the Issues of Health Care Today. University of California Extension, Berkeley, and Academy of Hospital Public Relations at Alumni House Lounge, University of California, Berkeley. Thursday-Friday. \$85. Contact: University Extension, University of California, 2223 Fulton Street, Berkeley 94720. (415) 642-4111.

April 17-18—Kern Postgraduate Conference. Kern County Medical Society at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: Milton L. Smale, M.D., Chairman, 1930 Eighteenth St., Bakersfield 93301. (805) 327-7637.

April 21-22—Eighth Annual Spring Symposium for Physicians Practicing General Medicine. Los Angeles County Heart Association and Los Angeles County Academy of General Practice at Ambassador Hotel, Los Angeles. Wednesday-Thursday. 10 hrs. Contact: Joyce Martin, Program Associate, LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

April 24—Community Health—Evolution, Revolution, Solution. UCSD at Revelle Campus Undergraduate Science Building, UCSD. Saturday. \$10. 6 hrs.

April 27-May 1—Hawaii Medical Association Annual Meeting. Ilikai Hotel, Honolulu. Tuesday-Saturday. New Challenges to Chronic Disease. Contact: H. Tom Thorson, Acting Exec. Dir., HMA, 510 S. Beretania St., Honolulu 96813. (808) 536-7702.

April 28-May 1—American College Health Association. Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: James W. Dilley, Exec. Sec., ACHA, 2807 Central St., Evanston, Ill. 60201. (312) 491-9775.

May 1—Facial Pain. PMC. Saturday.

May 1-2—Automation and Management in the Clinical Laboratory. UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

May 5-6—Team Problems in Intensive Care. PMC. Wednesday-Thursday. For physicians, nurses and administrators. \$35 single, \$75 team of three, \$90 team of four. 8 hrs.

May 7-8—Trauma. UCSF. Friday-Saturday.

May 8—Utilization Review in Hospitalized Patients. UCSF at St. Francis Hotel, San Francisco. Saturday.

May 8—Second Annual Clinical Pharmacology Symposium: Current Concepts in Drug Therapy for the Practicing Physician. STAN and Palo Alto Medical Clinic at Palo Alto Medical Clinic, Palo Alto. Saturday. \$15.

**CMA Postgraduate Institutes and Circuit Courses**

April 30-May 1—San Joaquin Valley Counties Regional Postgraduate Institute. CMA, UCLA and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. \$20. 13 hrs. Contact: CMA.

May 14-15—Redwood Regional Postgraduate Institute. CMA, STAN and Humboldt-Del Norte County Medical Society at Eureka Inn, Eureka. Friday-Saturday. \$20. Contact: CMA.

June 17-18—Sacramento Valley Counties Regional Postgraduate Institute. CMA, USC and Sacramento County Medical Society at Sahara-Tahoe Hotel, Lake Tahoe. Thursday-Friday. \$20. Contact: CMA.

May 12—Our Polluted Environment, Its Problems for the Clinician. Alameda-Contra Costa Chapter, American Academy of General Practice at Hilton Inn, Oakland. Wednesday. Clinical aspects of environmental pollution, illnesses of noise and crowding, environmental influences on future generations, what comes with the food we eat, diseases of dirty air, obstetrical and gynecological problems related to our current environment, a checklist for common environmental diseases. 8 hrs. Contact: Robert Taines, M.D., 2398 East Street, Concord 94520. (415) 684-8010.

May 15—Third Annual Symposium—Baldwin Hills Hospital. Proud Bird Restaurant, Los Angeles. Saturday. Refresher course for general practitioner. Medical emergencies in the office; cardiac shock, hematological emergency, cardiac emergency, drug interactions, respiratory emergency. 6½ hrs. Contact: Howard R. Bierman, M.D., Program Chmn., Baldwin Hills Hospital, 5525 W. Slauson Ave., Los Angeles 90056. (213) 645-2110.

May 22—Annual Seminar—General Hospital of Ventura County. Saturday. Contact: J. Austin Daly, M.D., General Hospital of Ventura County, Ventura 93003. (805) 648-6181.

May 22—Medical Alumni Reunion Clinical Symposium. STAN. Saturday.

May 23—Office and Lab Orientation: A Symposium for Medical Assistants. UCSF. Sunday.

May 27—Medical Centers of Africa. USC in Senegal, Ivory Coast, Ghana, Uganda, Kenya. Three weeks.

June 13-17—Western Area Conference of Foundations for Medical Care. United Foundations for Medical Care Service Corporation at Kauai Surf Hotel, Lihue, Kauai, Hawaii. Sunday-Thursday. Contact: Norman A. Brown, Exéc. Sec., 1625 Franklin Ave., Santa Rosa 95404.

June 30-July 4—Seminar for General Practitioners. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

July 16-17—Effective Medical Communication. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Friday-Saturday. \$225.

Continuously—Basic Science Correlation in Disease. VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.

Continuously—Ventura General Hospital Program. UCI and Ventura General Hospital at Ventura General Hospital, Ventura. Monthly lectures by UCI faculty. Contact: UCI.

Continuously—Postgraduate Medical Lecture Series—Orange County. UCI and Orange County Chapter, American Academy of General Practice at Saddleback Inn, Santa Ana. Monthly lectures by UCI faculty. May 10, Manipulative Bodily Therapy; June 4, Secondary Hypertension. Contact: UCI.

Continuously—Postgraduate Medical Lecture Series—Riverside-San Bernardino. UCI and Riverside-San Bernardino Chapter, American Academy of General Practice at Rams Horn Inn, San Bernardino. Monthly lectures by UCI faculty. April 15, General Plastic and Reconstructive Surgery; May 21, Diagnosis and Management of Bleeding Disorders. Contact: UCI.

Continuously—Educational Tape Service for Orthopaedists, Rheumatologists. Orthopaedic Audio-Synopsis Foundation. Monthly recorded teaching program on C-60 cassette tapes available to orthopaedic surgeons, rheumatologists and resident physicians. Twelve monthly tapes, annual subscription rate of \$72 (\$50 for residents). Contact J. Tonn, Managing Editor, Orthopaedic Audio-Synopsis Foundation, 6317 Wilshire Blvd., Los Angeles 90048. (213) 986-0131.

Continuously—Inter-Hospital Conference. UCSD and participating hospitals in the San Diego area at Radiology main conference room, UCSD. Weekly conferences conducted by various hospitals. Consult UCSD for dates and participating hospitals.

Continuously—Weekly Seminar for Graduate Students. UCSD at Basic Sciences Building, UCSD. Weekly Wednesday seminars, open to interested physicians. 12 noon.

Continuously—Dean's Day Program. UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. April 22, Community Medicine; May 27, Anesthesia; June 24, Neurology. Contact: UCSD.

Continuously—Biomedical Lecture Series. UCSD. April 21, May 19, 8:00 p.m., Basic Sciences Building, UCSD.

Continuously—Basic Science Lecture Series. UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.



**Continuously—Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

**Continuously—Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malpractice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MMN Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all California medical schools. Contact: Richard R. Getz, Exec. Dir., MMN, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

**Continuously—Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Prac-

ticing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Endocrinology-Metabolism, Gastroenterology, Hematology, Neurology, Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: April-May, June-July. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

**Continuously—Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, environmental radiation standards and nuclear power plants, overpopulation, abortion and contraception, technological problems of power generation in the United States, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and supersonic transport. Contact: John W. Farquhar, M.D., Assoc. Prof. of Medicine, STAN.

**Continuously—Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

### THE MISLEADING EEG SOON AFTER SEIZURE

"If you admit a child in febrile convulsions, status epilepticus, or prolonged focal fit, . . . your natural inclination is to order an EEG on him. But in a high percentage of cases, this will provide misleading information. The EEG records are often very slow, in a diffuse or focal way. Frequently you find misleading slow activity whereas if you wait a week—I'd say a week to ten days at least—you find a more representative kind of record. In other words, the first abnormality is simply a reflection of the insult to the brain of whatever happens during a severe seizure—whether it's anoxia, cerebral shock, or whatever you want to call it. The information is misleading. A week later you might find a petit mal kind of discharge or a focal kind of abnormality that's more important to you. If you don't wait, you wind up with EEG findings that look very bizarre. . . . Bearing this in mind will save you a lot of time and money."

—PATRICK F. BRAY, M.D., Salt Lake City  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Sphingolipidoses

FRANK M. YATSU, M.D., *San Francisco*

■ *Sphingolipidoses are an heterogeneous group of inherited disorders of lipid metabolism affecting primarily the central nervous system. These disorders occur chiefly in the pediatric population, and the degenerative nature of the disease processes is generally characterized by diffuse and progressive involvement of neurones (gray matter) with psychomotor retardation and myoclonus or of fiber tracts (white matter) with weakness and spasticity.*

*Biochemical research has identified the defects in the sphingolipidoses to specific lysosomal enzymes. For example, Niemann-Pick disease lacks sphingomyelinase; Krabbe's disease lacks galactocerebrosidase; Gaucher's disease lacks beta-D-glucosidase; metachromatic leukodystrophy lacks sulfatase; Tay-Sachs disease lacks hexosaminidase A; and generalized gangliosidosis lacks beta-galactosidase.*

*Although there are no currently available modes of rendering corrective therapy in these disorders, a definitive diagnosis is possible both antepartum as well as postpartum. This information provides a sound and accurate basis for genetic counseling.*

THIS REVIEW WILL FOCUS upon recent advances in neurochemistry of the sphingolipidoses. The term sphingolipidoses refers to a group of inherited disorders of lipid metabolism affecting chiefly the nervous system. The clinical problems have stimulated a wealth of productive research in neurochemistry, particularly in the areas of brain lipids and membranes. These investigations have also provided a foundation for future research into the molecular basis of nor-

mal brain function and structure. This review will describe briefly the current neurochemical information regarding the following sphingolipidoses: Niemann-Pick disease, Krabbe's disease, Gaucher's disease, metachromatic leukodystrophy, Tay-Sachs disease, and generalized gangliosidosis.<sup>1-4</sup> (See Table 1.)

## Clinical Aspects

The sphingolipidoses are a heterogeneous group of diseases and the diagnosis on clinical grounds is oftentimes difficult. However, a clinico-pathological approach is possible with these as well as other so-called degenerative diseases of the central nervous system.

These diseases can be divided into those that have primarily gray matter symptoms and signs

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TABLE 1.—*Sphingolipidoses*

		<i>Lipid</i>	<i>Enzyme Defect</i>	<i>Disease</i>
CERAMIDE +	—P-choline (phosphorylcholine)	= sphingo- myelin	sphingomyelin- ase	Niemann- Pick**
	—galactose	= galacto- cerebro- side	galactocere- brosidase	Krabbe's
	—glucose	= glucocere- broside	$\beta$ -D-glucosidase	Gaucher's
	—gal-SO <sub>4</sub>	= sulfatide	sulfatase	M.L.D. (sulfatide lipidosis)
	—Hexoses			
	—trihexose	= ceremide trihexoside	ceremide tri- hexosidase	Fabry's
	—hexoses + NANA*	= gangliosides: G <sub>M2</sub> ganglioside	Hexosaminidase A	Tay-Sachs***
CERAMIDE =		G <sub>M1</sub> ganglioside	$\beta$ -galactosi- dase	General- ized ganglio- sidosis
	fucose		fucosidase	Fucosidosis
	sphingosine + fatty acid	palmitic acid + serine		

\*NANA=N-acetylneuraminic acid

\*\*There are 4 clinically separate forms of Niemann-Pick and only type A is referred to above.

\*\*\*There are now 5 gangliosidoses with varying ganglioside and lysosomal enzyme deficiencies.

and those with primarily white matter symptoms. With the former, the gray matter symptoms and signs are those of either "irritation," such as seizures, particularly myoclonic seizures, or "inhibition," such as apathy, lethargy and dementia. Further, if occipital neurons are involved, cortical blindness will supervene. With diseases affecting primarily the white matter, the symptoms and signs are those of long-tract involvement; for example, spastic weakness with involvement of the corticospinal tract, pseudobulbar palsy with damage to the corticobulbar tract, incoordination from destruction of cerebellofugal fibers, and even cortical blindness, secondary to interruption of the optic radiations. Tay-Sachs disease would be a prototype of a disease affecting primarily gray matter, while metachromatic leukodystrophy would be more typical of disease predominantly of white matter.

### Niemann-Pick Disease

Niemann-Pick disease<sup>5-7</sup> is a genetic disorder subdivided into four groups depending upon the age of onset and clinical manifestations. The in-

fantile form or Crocker's type A accounts for approximately 85 percent of the cases of Niemann-Pick disease and definitive lipid abnormalities in brain are limited to this subgroup. The infantile form of Niemann-Pick disease is characterized clinically by psychomotor retardation with mental deterioration, seizures, spasticity, hepatosplenomegaly and frequently the presence of a "cherry red spot" in the fundi. (The "cherry red spot" is seen in several of the lipid storage diseases and is not diagnostic of any one entity.)

Pathological examination of enlarged visceral organs, brain and bone marrow discloses the presence of "foam cells" laden with lipid material. Analysis of the lipid reveals an abundance of sphingomyelin. An enzymatic mechanism that accounts for the abnormal intracellular deposition of sphingomyelin—that is, excessive synthesis or inadequate breakdown—was established by the discovery that patients with this disease lacked the hydrolytic enzyme sphingomyelinase.<sup>6</sup> As with other similar disorders, it is anticipated

that future research will provide a rational means by which to "induce" the deficient enzyme or prevent the abnormal accumulation of the lipid.<sup>1</sup>

### Krabbe's Disease

Krabbe's disease<sup>8-12</sup> is an autosomal, recessive, genetic disorder affecting primarily the central nervous system. Following normal early development, the disease has its onset during the middle of the first year of life. Symptoms are those of psychomotor retardation, tonic seizures, spasticity and blindness. Recently peripheral neuropathy has been described.

Histological examination of brains disclose diffuse demyelination of white matter with arcuate fiber sparing. In addition, there is the characteristic accumulation of large epithelioid or "globoid" cells in the white matter and hence its non-eponymic title of "globoid cell leukodystrophy."

Lipid analyses of brains affected with Krabbe's disease have given conflicting results, but separation and analysis of globoid cells indicate a higher relative concentration of cerebroside. This cerebroside's sugar moiety is galactose and hence is termed galactocerebroside. The proposal that a focal accumulation of galactocerebroside may account for the disease is supported by experimental studies involving the intracerebral injection of galactocerebroside. Dogs injected in this fashion developed neurological deficits associated with typical epithelioid or globoid cells in white matter.

A postulated enzyme defect in this disorder is unique, because it is in the synthetic as opposed to the more common catabolic pathway. The deficient enzyme is the cytoplasmic cerebroside, sulfotransferase. This enzyme transfers sulfate from the donor PAPS (phosphoadenosinephosphosulfate) to the 3-carbon of the galactose molecule of cerebroside. A genetic disorder in dogs manifesting similar histological and biochemical alterations as globoid cell leukodystrophy should help to clarify the molecular pathogenesis of this disease and offer a laboratory model for possible means of therapy. Recently, however, Suzuki<sup>12</sup> has accumulated compelling evidence in human brain tissue that the metabolic defect in Krabbe's disease is in fact a catabolic enzyme, namely, the lysosomal galactocerebroside- $\beta$  - galactocerebrosidease.

### Gaucher's Disease

Gaucher's disease<sup>13-15</sup> is an autosomal, recessive genetic disorder that has its onset in infancy or adulthood and infrequently during adolescence. The infantile form characteristically affects the central nervous system and is sometimes referred to as the "cerebral form" of Gaucher's disease. Clinically this disease is similar to Niemann-Pick disease in its presentation with psychomotor retardation, poor feeding due to bulbar weakness, opisthotonus, spasticity, and striking hepatosplenomegaly. Death ensues in the first year of life in a decerebrate state.

Histologically affected tissues contain large, multinucleated cells with a characteristic dull, waxy appearance. The lipid accumulation is due to cerebroside. Since the sugar moiety is glucose, it is designated a glucocerebroside.

Investigations for an enzyme defect have revealed an absence of lysosomal beta-D-glucosidase, essential for the normal degradation of glucocerebrosides.

### Metachromatic Leukodystrophy

Metachromatic leukodystrophy<sup>16-21</sup> (MLD or sulfatide lipidosis) is an autosomal, recessive, genetic disorder known since 1910 that becomes manifest during childhood and occasionally in adulthood. The symptoms in childhood are those of leukodystrophy, in that motor symptoms predominate. Muscular weakness and wasting, associated with a stumbling gait or *genu recurvatum*, may be the initial symptom.

MLD is unique among the sphingolipidoses because the peripheral nervous system is affected. Thus, evidence of a peripheral neuropathy with sensory, motor, and reflex changes may precede or supersede the findings of a leukodystrophy. With progression of the disease, generalized cerebral dysfunction develops. Seizures occur in one-half the patients, blindness in one-third, and death follows a decerebrate or decorticate state. The adult form of MLD usually presents as an organic dementia or psychosis, frequently diagnosed as schizophrenia. These patients, however, eventually manifest diffuse central nervous system involvement with corticospinal, corticobulbar, and cerebellar symptoms.

Histochemical studies disclose the presence of intracellular lipids, not only in the central and peripheral nervous systems, but also within visceral organs, such as kidney, liver, and gallblad-



der. Impairment of these organs does not become clinically apparent. Characteristic staining is metachromasia—that is, an alternate color to the dye used, such as toluidine blue staining red or cresyl violet staining brown. In addition to the deposition of sulfatide within white matter cells, there is symmetrical demyelination of white matter with U-fiber or arcuate fiber sparing. Intraneuronal collection of metachromasia is not characteristic except for few Betz cells and for certain subcortical neurones, notably the cerebellar dentate nucleus.

Identification of sulfatide as the lipid responsible for metachromasia in MLD was first demonstrated in 1958 by two independent workers, Austin in the United States and Jatzkewitz in Germany. Lipid analyses in MLD reveal a ten-fold increase in brain sulfatide concentration with an inversion of the sulfatide: cerebroside ratio to 4:1. Normally the ratio is approximately 0.25 to 1. Analysis of the lipid composition of myelin in MLD demonstrates a preponderance of sulfatide; this has led to the speculation that demyelination in this disease may be due to formation of an unstable membrane. O'Brien reasoned that the preponderance of sulfatide in the myelin membrane could lead to a less cohesive membrane because of abnormalities in the surface charge of the membrane, due to an excess of electronegatively charged sulfate groups. MLD appears to be one of the first examples of a disease resulting from a molecular defect in membrane structure.<sup>18</sup>

Although the clinical diagnosis of MLD is suggested by the presence of leukodystrophic symptoms and signs combined with a peripheral neuropathy, the definitive diagnosis is established by one of several techniques. The older technique of demonstrating metachromatic granules in the urine with toluidine blue can give false-positive results, since other substances besides sulfatides (mucopolysaccharides, for example), are metachromatic. A sensitive and accurate test devised by Austin is detection of arylsulfatase in urine. Affected persons have no enzyme activity. Alternatively, biopsy of a nerve, such as sural nerve, with demonstration of metachromasia would establish the diagnosis of MLD. Biochemical studies on tissues from MLD have identified an absence of sulfatase, the lysosomal enzyme which hydrolyses the sulfate group from sulfatide. Clinical investigations of sulfated compound reveal a slow turnover in MLD compared to normal subjects. These

findings would support *in vitro* biochemical data of defective catabolism of sulfatide.

Attempts to restrict sulfur intake and thereby the available precursor pool for sulfatide synthesis or the infusion of the missing enzyme sulfatase have been unsuccessful in altering progression of the disease in clinical trials. Knowledge that vitamin A is a required cofactor in the synthesis of PAPS (phosphoadenosinephosphosulfate) has raised the possibility of inducing vitamin A deficiency in MLD to decrease the available activated sulfate for sulfatide synthesis.

Clinical application of this proposal would appear to have impracticalities, but information to date is insufficient.

## Tay-Sachs Disease

Tay-Sachs disease<sup>22-28</sup> or infantile amaurotic familial idiocy (AFI) is a genetic disease occurring primarily in Jewish infants. The disorder commences during the middle of the first year of life after an apparently normal early development. Death ensues after a period of two to four years. The brunt of the disease is upon the central nervous system, particularly the grey matter. As the name implies, amaurosis develops, and the so-called "cherry-red spot" of the macular region is to be seen on fundoscopic examination and idiocy is concomitant. In addition, grey matter involvement gives rise to a cortical irritative phenomenon, manifested by myoclonic seizures. Pathological examination reveals "ballooned" neurones filled with lipid staining material. Electron microscopic studies of the involved neurones disclose the cytoplasm to be filled with membranous, lamellated bodies termed "membranous cytoplasmic bodies" or MCBS. Lipid analysis of these bodies, obtained by differential centrifugation, reveals an increase of monosialoganglioside. This ganglioside which lacks the terminal galactose is normally found in very small quantities and is referred to as the "Tay-Sachs ganglioside" or GM<sub>2</sub> ganglioside (Svennerholm's nomenclature). The enzymatic defect in Tay-Sachs disease is now known to be an absence of a lysosomal beta-D-N-acetylhexosaminidase.<sup>8</sup> An as yet unexplained and unconfirmed finding in Tay-Sachs disease is decreased activity of serum fructose-1-phosphate-aldolase.<sup>23</sup> Recently, O'Brien and Okada have taken amniotic fluid of suspected carrier mothers and applied tissue culture techniques to grow fibroblasts upon which enzyme

TABLE 2.—*Diagnostic Tests for Sphingolipidosis*

<i>Disease</i>	<i>Blood</i>	<i>Tissues</i>	<i>Other</i>
<i>Laboratory Diagnosis</i>			
Niemann-Pick	vacuolated lymphocytes	foam cells in marrow, involved viscera	
Krabbe's		brain* and peripheral nerve biopsy	elevated CSF protein
Gaucher's	deficient Beta-glucosidase in WBC or skin	Gaucher's cells in marrow and involved viscera	
MLD (sulfatide lipidosis)	decreased WBC sulfatase	peripheral nerve biopsy showing metachromasia	urinary sulfatide increase or sulfatase decrease
Tay-Sachs	absent hexosaminidase A in serum & WBC	rectal and/or brain* biopsy; fibroblast from skin; prenatally by amniotic fluid cell assay	elevated CSF protein
Generalized gangliosidosis	deficient beta-galactosidase in WBC	brain* and/or visceral biopsy; foam cells in marrow	deficient beta-galactosidase in urine

\**Brain Biopsy.* Establishment of a definitive diagnosis with the use of brain biopsy is justified for genetic counseling provided the patient demonstrates irreversible dementia and that adequate neurosurgical, histological and biochemical facilities are available.

analyses are made. The diagnosis of Tay-Sachs disease may be possible before birth by finding a deficiency of hexosaminidase.<sup>25</sup> This technique of amniocentesis holds great promise as a powerful diagnostic tool and opens doors for its utilization for antepartum diagnosis in other genetic disorders.<sup>26,28</sup>

### Generalized Gangliosidosis

Generalized gangliosidosis (or GM<sub>1</sub> gangliosidosis, type 1)<sup>29-31</sup> is an acute infantile disease characterized by psychomotor retardation, hepatosplenomegaly, and coarse features similar to those of Hurler's disease. Generalized gangliosidosis is due to an accumulation of GM<sub>1</sub> ganglioside in brain and viscera as well as mucopolysaccharide in the latter. Death ensues in the first two years of life. The disease has been confused with Tay-Sachs disease because of the finding of a cherry red spot in the macula and psychomotor retardation, with Hurler's disease because of the presence of similar phenotypic abnormalities. Enzymic studies disclose a pronounced deficiency of beta-galactosidase which accounts for accumulation of the GM<sub>1</sub> ganglioside and the mucopolysaccharide. There is as yet no specific form of therapy but early recognition and diagnosis is important so that accurate genetic counseling can prevent similar births.

Juvenile GM<sub>1</sub> gangliosidosis (or GM<sub>1</sub> gangliosidosis, type 2) has as its onset about age one and is due to the cerebral but not visceral accumulation of GM<sub>1</sub> ganglioside. Death ensues within

three to ten years. Although beta-galactosidase is also absent in this disease, it is phenotypically distinct from generalized gangliosidosis because of the absence of visual disturbances, cherry red spot of the macula, hepatosplenomegaly, and significant bony deformities. (Late infantile amaurotic idiocy or Jansky-Bielschowsky disease is phenotypically distinct from generalized gangliosidosis and does not represent a sphingolipidosis.)

Table 2 shows diagnostic tests for the identification of various kinds of sphingolipidoses.

### Neurochemistry of Brain Lipids

The brain is 80 percent water, yet of the dry weight, brain lipids are the major constituent (60 percent and are classified into three main groups: (1) the sterols, primarily cholesterol, (2) the phospholipids, and (3) the sphingolipids. The major types of sphingolipids are gangliosides, cerobrosides, sulfatides, and sphingomyelin. Sphingolipids constitute approximately 10 percent of whole brain lipids and approximately 20 percent of purified myelin lipids. Of interest is the localization of gangliosides in neurons and their virtual absence in myelin.

The sphingosine molecule is an essential constituent for the structure of sphingolipids from which it derives its name. Sphingosine is synthesized from the condensation and subsequent decarboxylation of palmitic acid and serine to form an 18-carbon amino-sugar. The three main groups of lipids noted above of cholesterol, phospholipids, and sphingolipids are assembled with pro-



tein moieties to form membranes and become the structural boundary of cells and their subcellular organelles. A postulated structure of membranes is that of a "bimolecular leaflet" with interdigitation of opposing lipid molecules. This concept was derived from electron-microscopic and x-ray diffraction data.

Anatomically, gangliosides are associated primarily with neurons, or "ganglion" cells, from which they derive their name. This highly polar lipid plays an important role in neuronal function, but its precise nature is as yet unknown. Subcellular fractionation of nerve cells has yielded information that gangliosides are associated primarily with microsomes and synaptosomes. Gangliosides are distinct from other sphingolipids by containing one or more N-Acetylneuraminic acid (NANA) molecules, the biologically most significant member of the family of sugars called sialic acid. Ten separate gangliosides have so far been identified, depending on the number of attached NANAs (1 to 3), their combination, and the number of attached hexoses. Over 90 percent of the gangliosides are accounted for by four major gangliosides: one monosialoganglioside (different from the Tay-Sachs ganglioside which lacks a terminal galactose), two disialogangliosides, and one trisialoganglioside. The complex nature of gangliosides is suggested by their dependence upon protein synthesis, since ganglioside synthesis is inhibited by puromycin, an inhibitor of protein synthesis.

Although sphingomyelin contains the word "myelin," it is not found exclusively nor abundantly in myelin and, therefore, is a misnomer. Cerebroside, on the other hand, is found in relative abundance in myelin and is frequently considered a "marker" of myelin lipids.

Normally, myelin contains three to four times as much cerebroside as sulfatide. Sulfatide is a sulfate ester of cerebroside and is synthesized by the addition of sulfate to cerebroside from the activated sulfate, phosphoadenosine-phosphosulfate (PAPS), by the cytoplasmic enzyme, cerebroside sulfotransferase.

This brief review has summarized the current knowledge of the biochemical abnormalities in the sphingolipidoses. Elucidation of this heterogeneous group of rare diseases of the central nervous system has followed the traditional sequence of clinical characterization, pathological verification, chemical analysis, and finally the biochemi-

cal identification of the enzymatic defect. These "experiments of nature" have provided a biochemical insight into the complexity of the nervous system. It is anticipated that continued exploration of these and similar disorders of brain will yield rational clues to their therapy as well as shed light on the molecular basis of normal neural function.

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# Marijuana: A Realistic Approach

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■ *Much of the current confusion concerning marijuana has been caused by a lack of definition of terms. Variations in drug effect that are related to the type and potency of cannabis preparation and route of administration need clarification.*

*When domestic strength marijuana is smoked recreationally, the subjective effects include relaxation, mild euphoria and increased sensory awareness. The objective effects include tachycardia, reddening of the conjunctivae and a distorted sense of time. Undesirable effects such as panic reactions, amotivational behavior, and acute toxic psychosis occur infrequently and are reversible with proper therapy. Other effects which have been attributed to marijuana are unsubstantiated.*

*The recent upsurge in use of marijuana involves persons of a different type than those who used it heretofore and has greatly increased the number of people familiar with the drug. The disparity between what many people know empirically and the information disseminated through official media has lessened the credibility of physicians with many of our younger citizens. When young people recognize misinformation about marijuana, they are no longer listening when the facts are presented about more dangerous drugs, and the abuse of these drugs must be our main concern. To be considered is the potential hazard to adolescent users who may concomitantly be exposed to a subculture of experimentation with stronger drugs at a time when the opinion of a peer group is a strong factor in their behavior.*

THE ABUSE OF DANGEROUS DRUGS in this country is a growing problem which has not received the medical recognition and response that it deserves. When physicians have become involved with the problem, their efforts are too often ineffective. Unfortunately, the credibility of physicians is diminished with the young people most in need of

drug education, and this is largely due to the viewpoint on marijuana generally associated with the medical profession. Too many physicians have employed the traditional arguments against marijuana without first reviewing them for authenticity and applicability. In so doing, they fail to realize that many of these assertions are contradicted by the personal experience of a growing number of our younger citizens. It is becoming apparent that such an approach can only hamper

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our total drug education effort, because when young people recognize misinformation about marijuana, they are no longer listening when the facts are presented about more dangerous drugs.<sup>1,2</sup> It is urgent for physicians and drug educators to develop a realistic approach to marijuana by reviewing the recent controlled research in this area and by acquainting themselves with the current sociological context of its use.

## Marijuana

Marijuana is a mixed preparation of the flowering tops, leaves, seeds, and stems of the hemp plant, *Cannabis sativa*. The flowering tops of both the male and female plants produce a sticky resin which contains tetrahydrocannabinol or THC, the major pharmacologically active ingredient.<sup>3</sup> The potency of the mixture depends on resin content and this is determined mainly by plant strain but also by factors involved in cultivation, harvesting, and preparation of the crop. The highest quality marijuana is derived from choice hemp grown in hot, humid climates with a final mixture containing mostly resin-covered tops and upper leaves.<sup>4,5,6</sup>

Most of the marijuana in this country is either imported from northern Mexico or grown locally, and its THC content varies from near zero to 1.5 percent.<sup>7</sup> Marijuana from more tropical areas is generally stronger. According to the Army Chemical Laboratory in Japan, "Viet Nam Green" from Southeast Asia is twice as potent as our domestic variety.<sup>8</sup> "Acapulco Gold" grown in southern Mexico may contain as much as 2 to 4 percent THC. "Panama Red" imported from the Canal Zone is reputedly the strongest marijuana of all. Because of variations in potency, it is important to specify THC percentage before considering pharmacological effects, keeping in mind that the marijuana generally available in this country is approximately 1 percent THC.

## Hashish

Hashish is the cannabis product obtained by separating the pure resin from the remainder of the plant. Pure resin can contain as much as 20 percent THC, so hashish can be up to ten times stronger in effect than the most potent marijuana regularly available in the United States.<sup>5,9,10</sup> This difference in potency explains why hashish can produce hallucinations while such dramatic ef-

fects are not observed when domestic strength marijuana is smoked recreationally. Hashish effects are often incorrectly attributed to the weaker mixed product, so it is important to regard the two as separate entities, especially when reviewing the literature on cannabis from other countries.

## THC

Tetrahydrocannabinol or THC is generally considered the main pharmacologically active principle of marijuana. In addition to being extractable from cannabis resin, THC can be synthesized, and it is currently being employed in research. Isbell studied the effects of synthetic THC on former marijuana smokers and found that these patients had an increase in resting pulse rate and became subjectively "high" after an ingested dose of 120 mcg per kg of body weight, or a smoked dose of 50 mcg per kg. He concluded that delta-9-THC accounts for most if not all of the psychotropics of marijuana.<sup>11,12</sup>

In light of the fact that a white powder labelled THC has been sold on the street for only \$2.50 per capsule, it should be kept in mind that THC is difficult to manufacture and costs \$50 per psychoactive dose. On analysis this material sometimes contains methamphetamine, mescaline or LSD, but usually it turns out to be phenylcyclohexylpiperidine or PCP (sernyl, the "peace pill"), a veterinary anesthetic. Smith reported the case of a patient supposedly overdosed with THC who was treated with a phenothiazine tranquilizer because his physician had read that large amounts of THC could cause hallucinations. Unfortunately this patient was actually overdosed with PCP and the additional depressant led to coma, respiratory arrest, and death.<sup>13</sup> It is important to remember that any patient supposedly overdosed with synthetic THC has almost certainly received something else, so treatment should be based on the symptoms and not the history.

## Route of Administration

In this country, cannabis products are usually smoked, using a technique of deep inhalation followed by breath-holding, but they can also be ingested after incorporation into food or beverages. Generally speaking, smoking provides a rapid, titratable induction of drug effect while ingestion delays the onset of action for 45 to 60

minutes. More specifically, the influence of route of administration on subsequent drug effects depends to some degree on the substance used. Isbell demonstrated that synthetic THC is more effective when smoked than when ingested.<sup>12</sup> It has been postulated that synthetic THC may undergo heat-isomerization to a more potent compound with the combustion of smoking.<sup>10</sup> With natural marijuana, however, a different response pattern is observed. According to Weil and others, ingesting natural cannabis products causes more powerful effects, more "LSD-like" effects, longer lasting effects, and more hangovers than smoking.<sup>1,6</sup> Weil also reports that he has seen ten cases of acute toxic psychosis resulting from ingested cannabis, but has never seen a case caused by the smoking of marijuana.<sup>14</sup> He raises the possibility that certain toxic constituents of natural cannabis resin that enter the body when the drug is eaten are destroyed by the heat of combustion.<sup>6,14</sup> These variations in response according to route and substance used should be considered before any conclusions drawn from research involving oral administration of THC are applied to marijuana usage in general.

### Subjective Effects

The subjective effects of marijuana usage are those which can be modified by the emotional set of the user and the mood of his immediate environment. When an experienced subject smokes domestic-strength marijuana in non-threatening surroundings for the purpose of reaching a "social high," the following subjective effects are produced. After a number of inhalations, a feeling of lightness develops in the extremities, followed by "rushes" of warmth and well-being that eventually lead to a sense of relaxation and mild euphoria. Sensory perception is heightened and accentuated but reality testing is not distorted. Lights seem brighter and colors appear more vivid. Certain sounds become striking in character and music takes on new dimensions. Appetite is sharpened and food and drink taste especially good. Time seems to stand still and there is an unusual ability to focus on a single object or event. Mental processes seem more acute and thoughts come rapidly. Through it all there is a curious feeling of being both involved and detached at the same time, and one feels that he can "pull himself together" and function normally if necessary. These effects are at their peak shortly after

smoking and they fade after a few hours, leaving a desire for sleep.

### Objective Effects

The objective effects of smoking domestic marijuana in a neutral laboratory setting were well described by Weil, Zinberg, and Nelsen in a double-blind controlled study which considered the variables previously discussed. They found that smoking marijuana containing 0.9 percent THC caused moderate increases in resting pulse rate, reddening of the eyes from dilatation of conjunctival blood vessels, and subtle difficulties in speech involved with remembering the logical thread of what was being said.<sup>15</sup> There was also a tendency toward overestimating the duration of a five-minute time sample. Contrary to popular belief, the pupils did not dilate. When mental functions and physical coordination were tested, the subjects who were smoking for the first time showed diminished performance, but the experienced users performed as well or better while "high." These effects were at their peak one half hour after smoking and gradually decreased until gone in three hours. From their results, the researchers concluded that marijuana, when smoked at the dose level usually found in this country, is a mild intoxicant producing minor, short-lived effects.<sup>6</sup>

More data is supplied by Crancer *et al.*, who tested subjects on an automobile driving simulator while recording errors in performance. Subjects tested while intoxicated with alcohol had a mean score of 97.44 errors, significantly higher than the control group score of 84.46. In contrast, the subjects tested while "high" after smoking marijuana (1.3 percent THC) had a mean score of 84.49, which is not significantly different from the control value.<sup>16</sup>

The effect of marijuana on auditory and visual sensation was studied by Myers and Caldwell in a neutral laboratory setting. Subjects were tested after smoking cigarettes containing either 300 mg of crude marijuana (1.3 percent THC) or carefully disguised placebo. The results indicated no significant difference in auditory or visual discriminatory ability between the two groups.<sup>17</sup>

The neurological and electroencephalographic concomitants of a marijuana "high" were investigated by Rodin, Domino, and Porzak. In their study, ten medical students who were experienced users smoked marijuana (1.3 percent THC) in a laboratory setting until they had reached their



usual "high." The observed effects were considered minimal. Results of the neurological examination remained normal with slight improvement in appreciation of vibratory sense. Mental status examination showed a slight decrease in intellectual efficiency, some excess jocularity, and slight loosening of associations. The ability to execute Bender-Gestalt drawings was hampered slightly after smoking. The electroencephalogram showed a slight but statistically significant shift toward slower alpha frequencies. There were no significant changes in cerebral evoked responses. The investigators concluded that the subjective pleasure and relaxation which follow the recreational smoking of marijuana are accompanied by a very slight decrease in highest cortical functions.<sup>18</sup>

The effects of cannabis extract on perception, learning ability, and coordination were evaluated by Clark and Nakashima using orally administered, highly concentrated marijuana resin in contrast to the previously mentioned studies which employed smoked marijuana. The performance of subjects on six out of eight tests was unimpaired even by high doses of the concentrated drug. The authors found impaired performance in the tests involved with complex reaction time and digit-code memory. In subsequent studies, they related the impairment in these two test areas to a measurable distortion of time sense.<sup>19,20</sup>

Tinklenberg et al conducted a double-blind controlled study to determine the effect of THC on cognitive tasks requiring recent memory. Calibrated doses of THC obtained by extraction from marijuana were administered orally to test subjects. The drug produced episodes of temporary impairment in recent memory that tended to be intermittent and brief in duration.<sup>21</sup>

## Undesirable Effects

The undesirable constitutional symptoms occasionally seen with recreational marijuana smoking are not of a serious nature. Bronchitis and asthma may occur in susceptible individuals and any treatment required is symptomatic. Nausea and vomiting occasionally develop when a novice smokes too much, disappearing as the drug effect wears off.<sup>10,13</sup>

A panic reaction to marijuana occurs when an individual becomes frightened of the effects of the drug and starts to doubt that these changes are reversible. Panic states are more common

among novice users who were ambivalent about trying the drug, and they are more frequent in areas where marijuana experimentation is considered deviant behavior. Panic is extremely rare in settings where marijuana is an accepted recreational intoxicant, especially among users who are receptive to its effects. Patients having panic reactions are able to demonstrate intact reality testing, so they should not be considered psychotic—merely frightened. According to Weil, treating them as psychiatric emergencies can actually prolong the panic by inadvertently confirming their fears of a mental breakdown. He said that medication and admittance to hospital are contraindicated except in cases of extreme agitation, and indicated that the best treatment is firm reassurance that the panic state is temporary and reversible as the drug effect wears off.<sup>14</sup>

An amotivational syndrome has been described in the small proportion of marijuana users who smoke heavily every day. Whether marijuana usage is a symptom, a contributory factor, or the primary cause of this syndrome is difficult to establish. In any event, the development of the syndrome is characterized by a progressive change from conforming, achievement-oriented behavior to a state of relaxed drifting. As a result, the person affected seems less willing to follow routines, endure frustrations or carry out long-range plans. In extreme cases greater introversion is exhibited, the subject becoming totally involved with the present while disregarding future goals. Persons in this condition tend toward child-like magical thinking and report greater subjective creativity but demonstrate less objective productivity.<sup>22</sup> Smith considers the condition reversible, indicating that if smoking is discontinued and underlying problems can be resolved, the user returns to his pre-drug level of functioning.<sup>13</sup>

An acute toxic psychosis (acute brain syndrome) is a temporary malfunction in reality-testing that occurs in response to a toxin. Such a reaction can be caused by many agents, including cannabis products. The toxic psychosis induced by marijuana is self-limited, usually requires no drug therapy, and is not dangerous if the patient is protected from injury for the duration of his disorientation. Weil reported having seen ten cases of acute toxic psychosis resulting from ingestion of cannabis products, but said he had never seen a case caused by the smoking of marijuana. He observed that, after a certain point is

reached, even smoking very potent marijuana continuously does not make the smoker any higher—only more sedated.<sup>14</sup> In contrast to this, Talbott and Teague reported 12 cases of toxic psychosis associated with marijuana smoking in Viet Nam. The authors indicated, however, that there is unusual environmental stress in Southeast Asia, and they also mentioned that about half of the already potent Vietnamese marijuana is adulterated with opiates.<sup>8</sup>

It has been charged that cannabis products can produce chronic psychotic states. Proponents of this indictment frequently cite reports from India and the Middle East, especially the work of Benabud of Morocco.<sup>23,24</sup> With specific reference to Benabud's report on the cannabis situation in Morocco in 1956, Mikuriya pointed out that the study was done without controls and that psychiatric diagnosis was obtained by copying admitting data.<sup>25</sup> When considering the symptoms which Benabud described as characteristic of "cannabis psychosis," Grinspoon indicated that they are common to other acute toxic states such as those associated with malnutrition and endemic infection, particularly in Morocco.<sup>9</sup> On a broader scale, Isbell referred to the reports from India and the Middle East as anecdotal clinical descriptions which are in most ways scientifically unconvincing.<sup>11</sup> Pillard indicated that these reports appeared to describe schizophrenic reactions in persons who also happen to be using cannabis.<sup>5</sup> Allentuck and Bowman denied the existence of a characteristic cannabis psychosis, and stated that marijuana will not produce psychosis *de novo* in a well-integrated, stable person.<sup>26</sup> Some support for this contention can be inferred from the fact that there is no evidence showing that psychosis is more prevalent among marijuana users than among non-users of the drug.<sup>5,9</sup> Well controlled, long-term studies in this field are needed before firm conclusions can be reached.

Hallucinations are not produced by the recreational smoking of domestic-strength marijuana, although such effects may follow the use of hashish or other concentrated cannabis products. This correlates with the data from Isbell's study using synthetic THC which determined that subjects became "high" after a smoked dose of only 50 mcg per kg of body weight, but there was no report of hallucinations until a dose of 200 to 250 mcg per kg was reached.<sup>12</sup>

Marijuana is not an addictive drug. Physical dependence and dose tolerance do not develop with its use, and withdrawal symptoms are not seen when usage is discontinued. The "psychic dependence" that may occur with marijuana can be classified as habituation, and it is not as strong as that seen with tobacco or alcohol.<sup>1,2,5,9,27,28</sup>

There is nothing inherent in the pharmacologic properties of marijuana which leads to the use of more dangerous drugs, particularly heroin. The fact that many heroin addicts have smoked marijuana does not establish a causal relationship, especially in view of the overwhelming majority of marijuana smokers who never use heroin.<sup>1,2,5,9</sup> Smith considers the "stepping-stone theory" invalid and maintains that any progression to stronger drugs that occurs is a result of personality and environmental factors and is not dependent on the pharmacological properties of marijuana.<sup>10</sup>

Marijuana does not cause aggressive criminal behavior.<sup>9</sup> As early as 1894, the Indian Hemp Drug Commission concluded that there was little or no connection between the use of hemp drugs and crime.<sup>29</sup> In 1946, Bromberg and Rodgers studied 40 users and 40 non-users of marijuana who were naval prisoners, and the non-users of the drug were shown to have committed more aggressive crimes.<sup>30</sup> Maurer and Vogel stated that the effects of marijuana are minor compared with those seen with the abuse of alcohol, and they expressed belief that cannabis has received a disproportionate share of publicity as an inciter of criminal behavior.<sup>27</sup> Chopra et al pointed out that the pacifying effect of cannabis on an individual serves as a deterrent to violent behavior.<sup>21</sup> This view is shared by McGlothlin and West, who agree that the characteristic non-aggressive response to marijuana would tend to inhibit rather than cause violent crime.<sup>22</sup>

Smoking marijuana does not lead to sexual debauchery. There is no evidence that cannabis is an aphrodisiac even though some users report greater enjoyment of sexual intercourse while "high." The reports most likely stem from the increased sensory awareness and the distorted time sense which would seem to prolong the duration of orgasm. Anyone who attempts to use marijuana as an adjunct to seduction, however, will generally be disappointed, for moral barriers remain intact.<sup>2,9,27</sup>



Concerning the genetic consequences of using cannabis products, there has been no case of human fetal damage attributed to marijuana alone.<sup>5</sup> Recent studies have shown that cannabis does not produce significant aberrations in chromosomes either *in vitro*<sup>31,32</sup> or *in vivo*.<sup>33</sup> On the other hand, in studies in which rats, hamsters, and rabbits received large parenteral doses of marijuana extract during early gestation, an increased incidence of fetal malformation and rejection was reported.<sup>34,35</sup> To keep such animal data in perspective, it should be noted that fetal malformations have been produced in mice under similar experimental conditions using comparable doses of common aspirin.<sup>36</sup> Even though the dose of extracted cannabis resin used in these animal experiments far exceeds the dose of marijuana ordinarily used by human subjects and despite differences in species response, it appears reasonable to caution women specifically against the use of marijuana during pregnancy.<sup>5</sup>

The possibility of cannabis-induced hepatotoxicity has been raised by Kew et al, who carried out an uncontrolled study of 12 marijuana smokers and found "evidence of mild liver dysfunction" in eight. Percutaneous liver biopsy in three subjects showed "striking parenchymatous degeneration." Unfortunately, there were no controls, and three of the test subjects were also users of alcohol while six took "pep pills" when available. A more carefully designed study must be done before firm conclusions can be reached in this matter.<sup>37</sup>

Marijuana is a non-lethal drug in human subjects. A high degree of safety has also been demonstrated in animal experiments. The median lethal dose (LD<sub>50</sub>) of synthetic THC in mice is 1500 mg per kg of body weight, and huge doses have been given to dogs without causing death.<sup>1,9,11</sup> There has been no reported case of fatal marijuana overdosage in man.<sup>1,9,38</sup>

### A Realistic Perspective

Before a realistic perspective can be developed, marijuana must be evaluated as a substance rather than as a symbol of the generation gap. The growing body of factual information must also be considered in relation to the current sociological framework in which marijuana is used.

At one time in this country, the use of marijuana was limited to jazz musicians, migrant farm laborers, and urban Negroes.<sup>6,11</sup> In recent years, how-

ever, its use has become widespread so that users and experimenters are now found in almost every sector of society.<sup>5,39,40</sup> As early as 1967-1968, Manheimer et al determined in a probability-sampled census-tract study of 1104 adult San Francisco residents that 13 percent of the total cross-sectional population had smoked marijuana; and in the age group 18 to 24, half the men and a third of the women reported previous experience with marijuana.<sup>39</sup> More recently, Hochman and Brill reported that 52 percent of the undergraduate students at UCLA have tried marijuana, while 34 percent use it once a week or more.<sup>41</sup> Studies performed in high schools over the past four years indicate a steady upward trend in marijuana usage, so that now in some schools it is difficult to find a pupil who has not tried it.<sup>1</sup> Clearly, then, the use of marijuana has become fairly common in this country, and the sociological implications of this large population which is familiar with the drug through personal experience or observation must not be underestimated. The disparity between what is known by so many people empirically and the information disseminated through official media has caused the medical profession and public officialdom to suffer a general loss of credibility with a growing number of our younger citizens.<sup>1,2</sup>

At one time, marijuana smokers were generally characterized as non-productive, sociopathic individuals, but the recent upsurge of marijuana usage among middle class Americans has rendered this appraisal invalid. In his San Francisco survey, Manheimer discovered that the majority of adult marijuana users were reasonably conventional people.<sup>39</sup> In their work at UCLA, Hochman and Brill found no difference between users and non-users with regard to number of interruptions in study, probations or suspensions. The marijuana users also had higher over-all grade averages, and twice as many users as non-users were going on to graduate studies and advanced degrees.<sup>41</sup> This latter trend is already in evidence at the UCLA School of Medicine, where, it is estimated, 75 to 90 percent of the medical students have had experience with marijuana.<sup>1</sup> We must recognize that instead of being characterized as non-productive sociopaths, many of today's marijuana users can be better described as socially perceptive, functioning individuals who offer a great deal of potential contribution to society.<sup>1,5,40,42</sup>

For many years, marijuana smoking was generally considered deviant behavior, but among the younger age groups in our current society, a different frame of reference is developing. In the youth culture, marijuana is smoked by individuals for its relaxant effects and by couples and groups as a social lubricant in much the same context as their elders use alcohol.<sup>2</sup> Vogl and others have noted that many young people no longer regard marijuana as a dangerous drug but classify it instead as a social intoxicant.<sup>2,43</sup> In 1968, a Michigan Health Department study involving 1379 high school seniors concluded that among young people the use of marijuana represents a social form of recreation far removed from the traditional problem of narcotic addiction.<sup>7</sup> It is important to recognize that the majority of the people in this country who currently smoke marijuana are occasional users who employ it in a recreational sense to reach a "social high" rather than a psychedelic experience.<sup>2,10</sup>

Marijuana itself was characterized by the Federal Bureau of Narcotics in the 1930's as a "killer drug" that caused "murder, insanity, and death"; but more recent controlled studies have shown that its effects are far less devastating than previously described.<sup>6,16-18,20</sup> What may be the greatest danger of marijuana is situational rather than biological and it applies more to younger users. Unlike adult recreational smokers, adolescent users are more likely to be introduced to a drug subculture where they encounter opportunities to experiment with stronger drugs at a time when the opinion of their peer group is a major determinant of their behavior. Although this is a potentially hazardous situation, it should not be used to justify the perpetuation of misinformation about marijuana, because such deception is self-defeating. When young people hear lies about marijuana, they are no longer listening when the truth is told about more dangerous drugs, and the abuse of these drugs must be our main concern.<sup>1,2</sup>

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# Australia Antigen and Liver Function Tests Following Infectious Hepatitis

## A Study of 111 Patients in Quest of Aids in Blood Donor Screening

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■ *An epidemic of infectious hepatitis involving 99 patients and employees of a state mental hospital revealed Australia antigen Au(1) to be absent from the blood of all but one of the subjects when tested at six weeks, three months, nine months and 12 to 18 months after onset of jaundice. The single patient with Au(1) at 12 months had no enzyme abnormality to indicate residual liver disease.*

*If Au(1) is the virus of hepatitis these data would support the concept that persistent or long standing viremia is not a feature of epidemic hepatitis. Moreover, results of this study suggest that the Au(1) test should not be used to establish the absence of a past history of hepatitis in blood donors. These data do not establish the value of the Au(1) test in blood donors with active viremia, but do suggest that of 111 patients with recent hepatitis 1 percent had persistent antigenemia and 4 percent probably had circulating antigen antibody complexes and constituted a potential risk to recipients of their blood. The degree of risk to recipients from transfused blood of post-hepatitis patients without demonstrable Au(1) cannot be assessed.*

ALTHOUGH IMPROVED TECHNIQUES in preparation of blood products and in selection of donors have reduced dangers to the recipient, the hazard of inoculation with hepatitis virus remains significant. This study was undertaken to evaluate one

potential blood donor screening test in a selected population of which each member had recently acquired icteric infectious hepatitis.

The incidence of anicteric hepatitis has been estimated to be more than 100 times that of icteric hepatitis.<sup>1</sup> Hence exclusion of prospective donors with a history of jaundice offers about 1 percent effectiveness in donor screening. Mirick,<sup>2</sup> in a review of post-transfusion hepatitis and gamma globulin, stated that more practical than the ad-

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ministration of gamma globulin in reduction of risk of post-transfusion hepatitis would be elimination of all but essential transfusions and the use of great care in the selection of blood donors. Commercial blood sources are thought to be associated with a far greater incidence of hepatitis in the transfused patient than are volunteer sources<sup>3,4,5</sup> and it has been estimated that exclusion of the commercial donor could result in 90 percent fewer cases of transfusion hepatitis.<sup>6</sup> Critical shortages of blood preclude elimination of the commercial donor today although effective screening tests may make donor blood safer.

Thymol turbidity tests have been advocated for blood donor screening.<sup>7,8,9</sup> In 1966 Bolin, Chase and Alsever<sup>10</sup> described a test for detection of antibodies against viral hepatitis that was positive in 30 percent of donors. They indicated that such a test is impractical because the rejection of 30 percent of potential donors (only one-third may be carriers of virus) would make it almost impossible for blood banks to fulfill the demand for blood. It has recently been suggested that complement fixation tests for Australia antigen and specific anticomplementary activity can be used to screen large numbers of blood donors for hepatitis carriers.<sup>11</sup>

Australia antigen, Au(1), is a particle 20 microns in diameter with morphologic characteristics of a virus.<sup>12</sup> It is said to be intimately associated with a hepatitis virus and may be on the virus.<sup>13</sup> Recent evidence suggests that Au(1) antigen is an antigen of a hepatitis virus which can cause acute and chronic hepatitis or can persist in asymptomatic carriers.<sup>12,14</sup> Au(1) has been identified in some patients with chronic diseases in which there is an impairment of immune function; included are lymphatic leukemia,<sup>15,16</sup> leprosy,<sup>17</sup> Down's syndrome,<sup>18,19,20</sup> and patients with chronic renal disease treated with hemodialysis.<sup>21,22</sup> Au(1) is found in 5 to 20 percent of apparently normal populations of some tropical climates<sup>23</sup> but is present in less than 0.1 percent of the United States population.<sup>24</sup> Au(1) has been identified in the serum of patients with chronic active liver disease with cirrhosis.<sup>25</sup> While Au(1) has been found in the serum of some patients with acute viral hepatitis, its presence is usually transient, a few days or weeks.<sup>13</sup> In some instances of prolonged hepatitis it may persist for months or years.<sup>26</sup> It appears in the blood before signs or symptoms of acute hepatitis appear and remains

in only about 7 percent of patients after recovery. The frequency of occurrence of Au(1) is greater in serum type hepatitis than in infectious hepatitis.<sup>24</sup> The antigen as determined by immunodiffusion testing has been identified in 41.1 percent of patients with post-transfusion hepatitis and 21.7 percent of patients with infectious hepatitis.<sup>12,27</sup> Other investigators report the incidence to be 34.1 and 13.1 percent respectively.<sup>28</sup> A recent study revealed Au(1) in 97 percent of 40 patients with serum hepatitis and absence of the antigen in 41 consecutive cases of infectious hepatitis.<sup>32</sup> In most instances Au(1) disappears as improvement occurs.<sup>12,14</sup> Hirshman et al<sup>29</sup> suggested that Au(1) appears to be a hepatitis virus and that a single virus group may be responsible for both infectious and serum hepatitis.

Identifying characteristics of two endemic forms of hepatitis were observed by Krugman and co-workers<sup>30</sup> in studies at Willowbrook State School in which newly entering inmates ingested material prepared from specimens obtained from diseased subjects. The short incubation agent, ms-1, caused apparent infectious hepatitis in 30 to 38 days while the long incubation agent, ms-2, caused a disease more like serum hepatitis in 41 to 108 days. Cross immunity between these agents was not demonstrated. Au(1) was identified in serum of only those patients inoculated with the ms-2 agent in a study by Giles et al.<sup>31</sup> Krugman and Giles<sup>32</sup> found that hepatitis-associated antigen was consistently present in serum from patients with ms-2 strain of serum hepatitis (sh) but was not present in ms-1 infectious hepatitis (ih). They also detected hepatitis-associated antigen earlier after a parenteral exposure to sh than after an oral exposure. The antigen appeared two weeks to two months before onset of jaundice and persisted for four months to 13 years in 35 percent of children. The sh antigen of Prince<sup>33</sup> is probably identical to Australia antigen.<sup>34</sup> In one study Au(1) was detected in 7.2 percent of blood donors. This rate is nearly that estimated for hepatitis carriers, 8.7 percent.<sup>23</sup>

Laboratory techniques for detection of Au(1), listed in order of increasing sensitivity or specificity, are agar gel diffusion, electronmicroscopic detection of sedimented antigen-antibody complexes, and complement fixation tests.<sup>24</sup> Fluorescent antibody techniques have revealed specific reactions between antibody to Australia antigen and an antigen on or within nuclei of liver cells.<sup>35</sup>



TABLE 1.—Summary of Abnormal Results of Various Tests

TEST	CHANGE	6 Wk. Test (111 pts.) ABNORMAL		3 Mo. Test (102 pts.) ABNORMAL		9 Mo. Test (92 pts.) ABNORMAL		12-18 Mo. Test (91 pts.) ABNORMAL	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total bilirubin . . . . .	Increased	19	17	3	2.8	3	3.8	4	4.4
Ceph flocculation . . . . .	Increased	73	66	60	59	46	51	38	42
Thymol turbidity . . . . .	Increased	10	9	8	7.7	0	0	0	0
Total protein . . . . .	Increased	10	9	18	17.1	5	5.4	5	5.5
Albumin . . . . .	Increased	14	12.6	20	19.6	1	1.1	3	3.3
Albumin-globulin ratio (A/G) . . . . .	Increased	30	27	28	28.5	7	7.6	9	10
A <sub>1</sub> globulin . . . . .	Decreased	16	14.4	28	28.5	12	13	9	10
A <sub>2</sub> globulin . . . . .	Decreased	26	23.6	15	14.7	12	13	6	6.6
B globulin . . . . .	Decreased	32	28.7	28	28.5	14	15.2	13	14.2
Globulin . . . . .	Decreased	3	2.7	3	2.9	1	1.1	1	1.1
S.G.O.T. . . . .	Increased	43	39	5	4.9	3	3.2	1	1.1
Alkaline Phos . . . . .	Increased	46	41	47	46	35	38	44	48
Au(1) antigen by complement fixation . . . . .		*3	2.7	0	0	0	0	1	1.1
Au(1) antibody by complement fixation . . . . .		0	0	0	0	0	0	0	0
Au(1) antigen by immunodiffusion . . . . .		0	0	0	0	0	0	0	0

\* Anticomplementary

## Methods

The study here reported was begun in 1960 by collecting blood from 111 patients with icteric hepatitis, 99 of whom were inmates or employees of a state mental hospital during an epidemic of infectious hepatitis in which 70 of the cases occurred in November and December of 1960. Initial specimens were obtained six weeks after onset of jaundice and repeated at intervals of three, nine and 12 to 18 months. Specimens were frozen and stored at  $-20^{\circ}\text{C}$  until large groups could be analyzed together. One hundred two patients were available for follow-up at three months, 92 at nine months and 91 at 12 to 18 months. Attrition in the number of subjects was due to discharges and transfers.

Laboratory tests included serum glutamic oxalacetic transaminase, alkaline phosphatase, total bilirubin, cephalin-cholesterol flocculation, thymol turbidity, total protein and albumin and plasma protein paper electrophoresis. These tests were completed within six to twelve weeks after freezing of specimens. Tests for Au(1) included complement fixation for antigen, complement fixation for antibody and agar gel immunodiffusion for antigen. These were performed on serum specimens that had been maintained in the frozen state for nine to ten years. Standard complement fixation<sup>11</sup> and immunodiffusion<sup>18</sup> techniques were

used. Positive and negative controls were used on each plate and each specimen was tested in duplicate.

## Results

Test results are summarized in Table 1. Indices of liver function of groups three months, nine months and 12 to 18 months slightly exceeded normal ranges.

Complement fixation for Au(1) was positive in only one specimen (1:16)—and this was one year after clinical jaundice. There were no previous specimens on this particular patient. Three specimens were anticomplementary and all others were negative at the six-week period. Complement fixation tests for antibody to Au(1) were negative in all 502 specimens. Immunodiffusion tests for Au(1) were negative in all samples.

## Discussion

All patients had clinical and biochemical evidence of infectious hepatitis at the onset of illness. All were jaundiced. All were considered by their physicians to have completely recovered before the third month serum specimens were obtained. There was no recurrence of jaundice in any patient during the period of study.

Interpretation of some results was made difficult because of exposure of most patients to tranquilizer drugs during observation. Persistence of

TABLE 2.—*Test, Methods and Normal Ranges Used in Study*

<i>Test</i>	<i>Methods</i>	<i>Normal Values</i>
Total bilirubin	Malloy-Evelyn	up to 1.6 mgm/100 ml
Cephalin-cholesterol flocculation	Hanger	0 to 2+ in 48 hours
Thymol turbidity	Shank-Hoagland	0 to 6 units
Alkaline phosphatase	King-Armstrong	0 to 11 units
SGOT	Reitman-Frankle	up to 40 units—males up to 35 units—females
Total protein	Kingsley	6.2 to 8.5 gms/100 ml
Albumin		3.5 to 5.5 gms/100 ml
Globulins		
Alpha <sub>1</sub>	Paper electrophoresis*	0.2-0.4 gms/100 ml
Alpha <sub>2</sub>		0.5-0.9 gms/100 ml
Beta		0.6-1.1 gms/100 ml
Gamma		0.7-1.7 gms/100 ml
Australia antigen by complement fixation	Shulman & Barker	Negative
Australia antibody by complement fixation	Shulman & Barker	Negative
Australia antigen by immunodiffusion	Allison & Blumberg	Negative

\*The spinco analytrol and Durum cells were obtained from Beckman Instrument Corporation—Fullerton, California

a relatively high incidence of abnormal cephalin-cholesterol flocculation tests in each period (66 percent at six weeks, 59 percent at three months, 51 percent at nine months and 42 percent at 12 to 18 months) may have been influenced by tranquilizer drugs which 68 percent of the patients with elevated values had received. Seventy-seven percent of patients with elevated alkaline phosphatase levels received tranquilizers. Tranquilizer drugs included phenothiazine derivatives (prochlorperazine, thioridazine, fluphenazine, promazine, trifluoperazine, chlorpromazine and perphenazine) and non-phenothiazine derivatives (chlordiazepoxide and rauwolfia derivatives). Three or more drugs were prescribed on an alternating schedule. Only one form of drug was given at any one time.

Craddock<sup>36</sup> said that jaundice appears in about 1 percent of patients treated with chlorpromazine in mental hospitals and liver function tests results are similar to those found with obstructive jaundice (elevated alkaline phosphatase and transaminase levels). This jaundice may appear several weeks after discontinuance of the drug and the alkaline phosphatase may remain elevated after the serum bilirubin has returned to normal. Wailzkin<sup>37</sup> found no correlation between levels of serum bilirubin and alkaline phosphatase in chlorpromazine induced jaundice.

Reduction of values for globulin fraction was seen to be nearly equally divided between patients treated with tranquilizers and those un-

treated. Depression of all fractions of globulin in patients receiving long-term tranquilizer medication has been reported.<sup>38</sup>

Cephalin flocculation and thymol turbidity tests have almost always been normal in patients with jaundice due to chlorpromazine.<sup>39</sup> The low incidence of abnormal thymol turbidity levels (9 percent at six weeks and 8 percent at three months) does not support the findings of others.<sup>7,8,9</sup>

All three instances of anticomplementary tests for Au(1) were in six-week specimens, and subsequent specimens for each patient were non-reactive. Anticomplementary activity may be due to a combination of antigen and antibody<sup>11</sup> or may reflect the presence of nonspecific reactants. There was only one patient with a positive complement fixation test, and the enzymes were normal in this case. Au(1) was not detected by less sensitive immunodiffusion tests in any of those found to be anticomplementary. Au(1) antibody by complement fixation was not detected in a single case. These findings suggest that, if Au(1) appeared early in the acute phase of infectious hepatitis in these patients, early disappearance is rapid as recovery occurs.

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## IMMEDIATE REPAIR FOR SECTIONED FACIAL NERVE

The patient has had a laceration of the face, and in exploring the wound you discover a sectioned facial nerve. What do you do?

"Immediate surgical repair is essential. The ends of the nerve can be approximated, especially if it's a clean incisional wound. It is much more difficult to try to repair a sectioned facial nerve after the area has been healed. Working through scar tissue makes it exceedingly difficult so I think that immediate repair at the time the laceration is sutured is indicated. The jagged lacerations are much more difficult to take care of than the clean incisional wounds, such as those from a knife or from glass, but they can be managed."

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# The Clinical Physiology of Calcium Homeostasis, Parathyroid Hormone, and Calcitonin

## Part II

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NOTE: Figures 1-6, Charts 1-22, Tables 1-3, and References 1-143 appear in Part I (March 1971) of this two-part article.

### Clinical Disorders of Calcium Homeostasis

#### *Primary Hyperparathyroidism*

Forty-five years after the first description of hyperparathyroidism<sup>144</sup> and 44 years after the first case ever treated in this country,<sup>145</sup> this endocrine disorder still presents challenging diagnostic and therapeutic problems.

In more than 90 percent of the cases, the disease is due to a solitary benign parathyroid adenoma; multiple adenomas, primary chief cell hyperplasia of all glands and, more rarely, parathyroid carcinoma are the underlying causes of hyperparathyroidism in the remainder of patients. At times, a histological differentiation between adenoma and chief cell hyperplasia cannot be made,<sup>146</sup> and in certain patients both abnormalities may be present. One of our recent patients presented with such a pathological com-

bination. The patient had persistent hypercalcemia (11.5 to 12.5 mg per 100 ml) and hypophosphatemia (less than 2.5 mg per 100 ml). At operation, one gland was normal, a second had oxyphil adenoma and the other two were enlarged and showed primary hyperplasia with an additional small oxyphil adenoma in one of them. The three diseased glands were removed, and the patient has been normocalcemic since. We and others have noted that in certain patients with parathyroid adenomas, the biopsy specimen from a normal gland may reveal distinct hyperplasia rather than normal histology or hypoplastic changes. These observations suggest that chief cell hyperplasia and adenomas may represent different stages of a single fundamental abnormality in the function of the parathyroid glands.

The majority of parathyroid tumors are located in the neck. Nathaniels et al reviewed the cases of 400 patients with primary hyperparathyroidism who were operated upon in the Massachusetts General Hospital since 1930.<sup>147</sup> They found that 80 percent of the patients had parathyroid tumors in the neck and only in about 20 percent, (84 patients) was the tumor located in the mediastinum—in the anterior in 67 patients and in the posterior mediastinum in 17. In 62 patients the tumor was successfully excised through a low collar thyroid incision, and in only 19 cases was mediastinotomy required. In 26 in-

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stances, the mediastinal parathyroid adenomas were found either within the capsule of the thymus or closely associated with it.

Biochemical and clinical manifestations identical to those noted in patients with primary hyperparathyroidism are seen in patients with malignant tumors which produce PTH. Among the tumors that may produce PTH, bronchiogenic carcinoma and renal cell carcinoma are the most common, although many other tumors have been reported to produce this syndrome.<sup>148,149</sup> It is of interest that a case of carcinoma of the breast which produces PTH has not been reported.

The biochemical and clinical manifestations of primary hyperparathyroidism caused by parathyroid adenomas are due to increased autonomous secretion rates of parathyroid hormone. Indeed, the levels of PTH in the blood in such cases, as measured by radioimmunoassay, have been found to be almost invariably elevated.<sup>6,57-59</sup> The secretory autonomy of parathyroid adenomas has been demonstrated both *in vitro* explants of adenomas<sup>143</sup> and *in vivo* studies in patients with parathyroid adenomas.<sup>57,58,98</sup> Incubation of the explants in hypo- or hypercalcemic media did not alter the concentration of PTH in the media. Furthermore, calcium or EDTA infusions to patients with parathyroid adenoma did not affect the level of PTH in their blood. In contrast, hypercalcemia, produced by calcium infusion, has been found to lower the level of PTH in patients with primary chief cell hyperplasia, indicating that such a hyperplastic gland is not functioning autonomously.<sup>150</sup>

Certain indirect observations made in our laboratory in patients with parathyroid adenomas suggest that such adenomas may not always display autonomous function.<sup>20</sup> The administration of inorganic phosphate to patients with parathyroid adenoma causes a fall in plasma calcium toward normal levels; however, while the patient still ingests phosphate, an escape from the control of plasma calcium may occur and hypercalcemia returns. This phenomenon is usually associated with further augmentation in renal  $\text{PO}_4^-$  clearance and decrement in renal  $\text{Ca}^{++}$  clearance, suggesting an increase in parathyroid hormone activity. It is possible that certain adenomas may secrete more PTH in response to the phosphate induced fall in serum calcium.

The main biochemical findings of primary hyperparathyroidism are hypercalcemia, hypo-

phosphatemia, increased renal clearance of  $\text{PO}_4^-$  and decreased renal clearance of  $\text{Ca}^{++}$ . All of these biochemical abnormalities are the result of the direct action of PTH on bone and kidney.

Hypercalcemia is the *sine qua non* for the diagnosis of primary hyperparathyroidism (Chart 23). The elevation in serum calcium may be mild, moderate or pronounced, depending on the type, size and rate of growth of the parathyroid adenoma.<sup>151</sup> Patients with parathyroid adenomas and normal serum calcium have also been reported.<sup>152,153</sup> The concept of "normocalcemic" hyperparathyroidism is based on the finding that the concentration of  $\text{Ca}^{++}$  in the blood remains consistently within the normal range. However, the value may be elevated for the individual patient. The authors know of no case in their experience or in the literature in which the level of  $\text{Ca}^{++}$  in the blood found before operation remained the same after the removal of the adenoma. In our personal cases, the concentration of  $\text{Ca}^{++}$  in blood always decreased significantly after operation. For example, the patient's normal or euparathyroid plasma  $\text{Ca}^{++}$  concentration is significantly lower than pre-operative value. It seems reasonable to conclude that for the isolated patient the diagnosis of "normocalcemic hyperparathyroidism" probably does not exist.

The concentration of inorganic phosphate in the blood is often low in patients with parathyroid adenoma, although cases in which serum phosphorus levels are normal are also encountered. It is likely that in most patients with primary hyperparathyroidism and with normal or minimal impairment of renal function, hypophosphatemia will be found when fasting blood specimens are correctly obtained. The blood should be free of hemolysis, collected with minimal stasis, and centrifuged within 10 or 15 minutes, and the plasma must be promptly separated from the red cells. If these precautions are not taken, phosphorus may leave the red blood cells and enter the plasma, causing a falsely high level of phosphorus in plasma. It should be emphasized again that hypercalcemia, *per se*, may cause hypophosphatemia. This may occur in patients with carcinoma of the breast and hypercalcemia. However, it should be mentioned that an association between carcinoma of the breast and parathyroid adenoma has been noted,<sup>154</sup> and the pres-

ence of an associated parathyroid adenoma might be responsible for the hypercalcemia and hypophosphatemia in some of these patients.

The renal clearance of phosphate is increased in most patients with primary hyperparathyroidism. This may be conveniently expressed as the percent of filtered phosphate excreted—for example: phosphate clearance ( $C_p$ )/creatinine clearances ( $C_{cr}$ ) X 100; or for further example, as the percent of tubular reabsorption of phosphate (TRP) which is  $(1 - \frac{C_p}{C_{cr}}) \times 100$ . The factors, other than PTH, which may affect renal phosphate handling have already been discussed.

Parathyroid hormone also lowers the renal clearance of calcium, and, therefore, in patients with primary hyperparathyroidism the degree of hypercalciuria, for any given elevation in plasma  $Ca^{++}$  concentration, is less than that seen in non-parathyroid hypercalcemic disorders (Chart 8).<sup>62-66</sup> In our experience, almost 50 percent of patients with primary hyperparathyroidism and normal renal function excrete less than 250 to 275 mg of calcium per 24 hours. To our knowledge, primary hyperparathyroidism in the presence of normal renal function is the only hypercalcemic disorder in which calcium excretion may be normal or only slightly elevated. Therefore, hypercalciuria is not a significant finding for the diagnosis of hyperparathyroidism; on the contrary, a normal or slightly elevated 24-hour excretion rate of calcium in a hypercalcemic patient is strongly indicative of hyperparathyroidism.

Patients with primary hyperparathyroidism have a wide variety of symptoms which are due to the effect of hypercalcemia on the functional integrity of the various organs. The changes of osteitis fibrosa cystica seen in the skeleton are again the result of the PTH action on bone.

When the classical biochemical, clinical and radiological findings are present, the diagnosis of hyperparathyroidism is easy, and no further diagnostic tests are required. It should be noted that hypercalcemia may be produced by a large number of pathological entities; and efforts should be directed toward the exclusion of other causes of hypercalcemia before the diagnosis of primary hyperparathyroidism can be made with confidence.



Chart 23.—Mean preoperative serum calcium values in patients with primary hyperparathyroidism. Broken lines represent normal mean expressed as regression with age; solid lines represent the 2.5 and 97.5 percentiles of normal group, respectively. Note that normal range so defined is different in men (upper) and women (lower) and it decreases with age in men but not in women. Each dot represents the mean preoperative value for a patient. Individual values would show somewhat more variation, with about 10 percent of cases showing one or more measurements within normal range. (Redrawn from Figure 1 of Keating, F. R., Jr.)



In patients with borderline biochemical findings and suggestive clinical history and manifestations, such as recurrent renal stones and peptic ulcer disease, certain diagnostic procedure may help to establish diagnosis. Measurement of the levels of PTH may offer the best diagnostic test. In patients with primary hyperparathyroidism the circulating levels of PTH are high, and a sensitive radioimmunoassay can detect these high concentrations of PTH. Such measurements may also be of value in the localization of an adenoma. Reiss and Canterbury<sup>150</sup> found that vigorous massage of the side of the neck where the adenoma is located caused a distinct rise in the circulating level of PTH. Reitz and associates<sup>155</sup> measured PTH in blood specimens which were obtained as they selectively passed a venous catheter along the cervical and innominate veins, superior vena cava and right atrium. Such a procedure may be helpful in localizing an adenoma which cannot be found in the neck.

Unfortunately, radioimmunoassay of PTH is not available as a routine laboratory procedure, and, therefore, one frequently finds it necessary to employ other procedures to arrive at a correct diagnosis. The following tests may be used:

1. *Calcium infusion:* Changes in parathyroid activity are reflected in alteration in TRP. If hypercalcemia produced by calcium infusion does not cause a decrease in phosphate excretion or a rise in TRP, one concludes that the parathyroid glands have lost the normal feedback response to changes in plasma  $\text{Ca}^{++}$  concentration that is, the glands have autonomous function and an adenoma should be suspected. The test, according to Kyle,<sup>156</sup> is done as follows: The  $(C_p/C_{Cr}) \times 100$  is measured on a 4-hour urine collection obtained between 8:00 a.m. and noon on day 1; 10 to 15 mg of  $\text{Ca}^{++}$  per kg body weight is then infused over 4 hours between 8:00 p.m. and midnight and urine is collected the following morning (day 2) between 8 o'clock and noon for the measurement of  $(C_p/C_{Cr}) \times 100$ . A fall of more than 50 percent in  $(C_p/C_{Cr}) \times 100$  occurs in normal subjects, while patients with parathyroid adenoma usually show less than a 40 percent fall in  $(C_p/C_{Cr}) \times 100$ . Chart 24 presents the response to calcium infusion in a group of patients with parathyroid adenomas before and after operation.<sup>157</sup>

Hyperactivity of the parathyroid glands occur in the very early stages of renal failure,<sup>108</sup> and this is associated with an increase

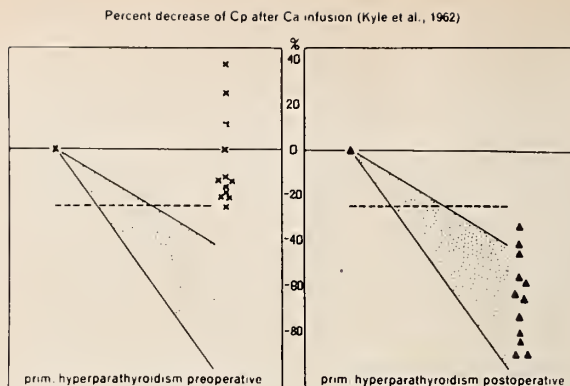


Chart 24.—Pre and postoperative results in primary hyperparathyroidism obtained with the calcium infusion method of Kyle et al. (Reproduced from Hass, H. G.<sup>157</sup>)

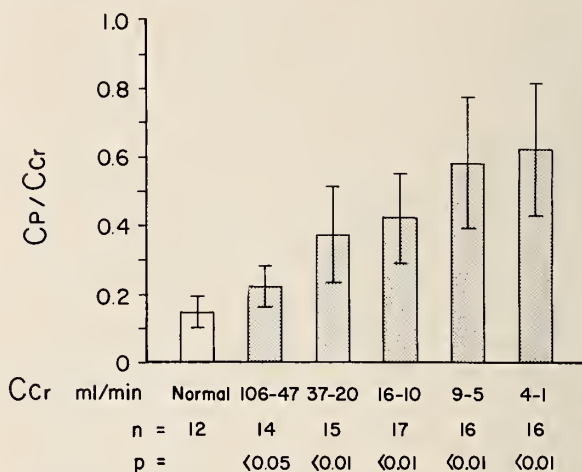


Chart 25.—Mean and SD values for the fractional excretion of filtered inorganic phosphorus ( $C_p/C_{Cr}$ ) at different levels of creatinine clearance ( $C_{Cr}$ ). n = number of patients, P refers to the relation between normal subjects and patients, as determined by t test.<sup>158</sup>

in renal phosphate clearance and a decrease in calcium clearance,<sup>158</sup> (Chart 25). Such a patient, especially if he has had renal stones, could be suspected as having "normocalcemic" primary hyperparathyroidism. However, such patients will respond in a normal manner to calcium infusion (Chart 26),<sup>159</sup> and, therefore could be readily separated from patients with parathyroid adenoma. In patients with more advanced renal failure ( $C_{Cr} < 40$  ml/min) calcium infusion loses its diagnostic significance.<sup>159</sup> The calcium infusion test is not necessary and should not be used in patients with definite hypercalcemia.

2. *Oral loading with inorganic phosphate:* The oral administration of inorganic phosphate

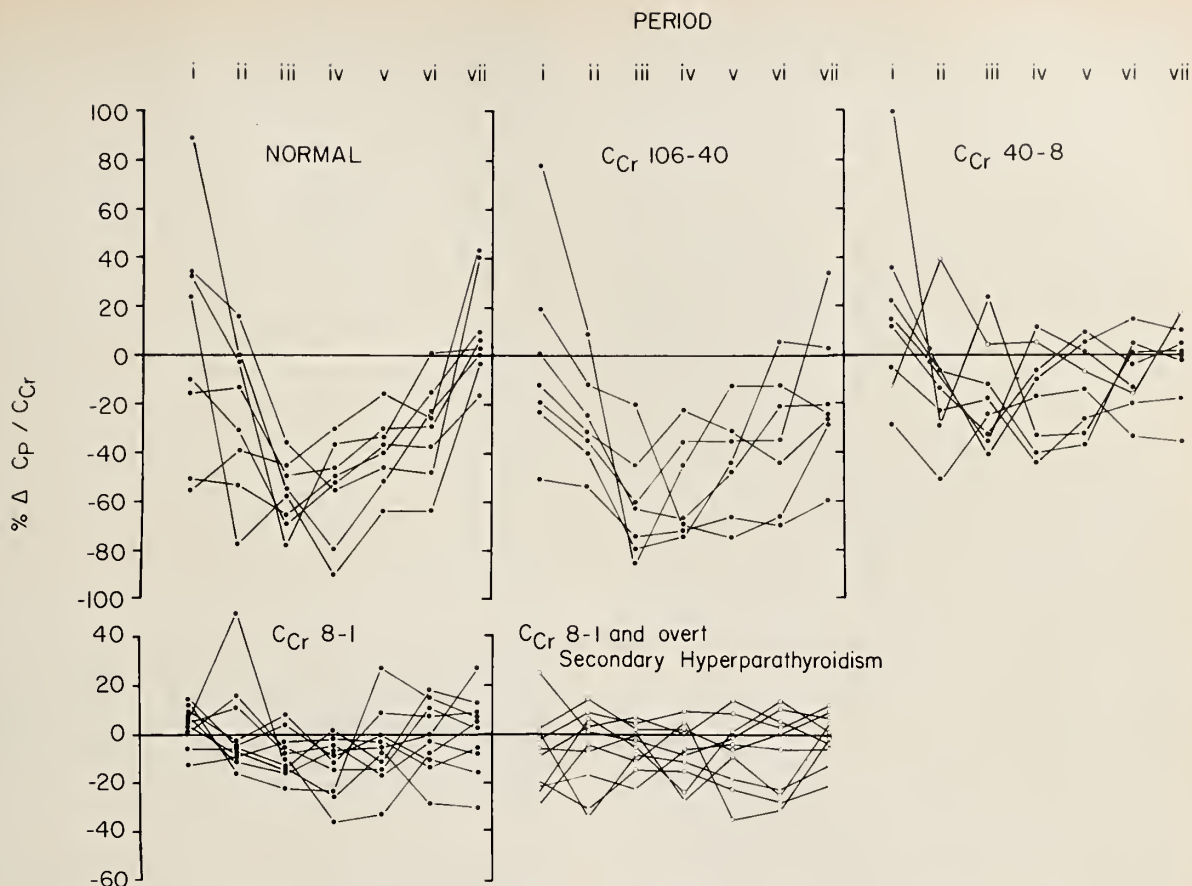


Chart 26.—The changes in fractional excretion of phosphorus observed after calcium infusion in both normal subjects and patients with renal failure. The data are expressed as percent change from the control value measured in the day preceding the infusion.  $C_{Cr}$ =endogenous creatinine clearance;  $C_p/C_{Cr}$ =fractional excretion of phosphorus;

$$\frac{\% \Delta C_p/C_{Cr} = \text{Pre-infusion } C_p/C_{Cr} - \text{Post-infusion } C_p/C_{Cr} \times 100}{\text{Post-infusion } C_p/C_{Cr}}$$

The numbers of the period indicate the time of urine collection after the calcium infusion: (i) between 8 p.m. and midnight (calcium infusion is given in this period); (ii) between midnight and 8 a.m.; (iii) between 8 a.m. and noon; (iv) between noon and 4 p.m.; (v) between 4 p.m. and 8 p.m.; (vi) between 8 p.m. and midnight (20 hours after the infusion), (vii) midnight to 8 a.m. (28 hours after infusion).<sup>159</sup>

for a few days may cause a greater increase in  $(C_p/C_{Cr}) \times 100$  in patients with parathyroid adenoma than in normal persons.<sup>20,77,160</sup> Twenty-four hour urine collections are obtained before and after five days of inorganic phosphate administration for the measurement of  $(C_p/C_{Cr}) \times 100$ . Two grams of elemental phosphorus are given in the first three days and 3 grams in the last two days. In most patients with primary hyperparathyroidism,  $(C_p/C_{Cr}) \times 100$  increases to 60 percent or more, while in normal persons  $(C_p/C_{Cr}) \times 100$  rarely exceeds 40 percent after this procedure (unpublished observations). Berge, et al<sup>161</sup> es-

tablished the diagnosis of hyperparathyroidism in seven patients with recurrent renal calculi, hyperealeiuria, hypophosphatemia and normal serum calcium on the basis of an increase in  $(C_p/C_{Cr}) \times 100$  after oral phosphate loading. In five of these patients the diagnosis was confirmed by the measurement of PTH level in their blood. This test should only be used in patients with normal or almost normal renal function since dangerous hyperphosphatemia may develop in patients with renal failure.

3. *Thiazide administration:* Administering thiazide diuretics causes a decrease in urinary calcium,<sup>162</sup> and these diuretics have been used



in the treatment of patients with recurrent renal calculi and idiopathic hypercalciuria.<sup>162</sup> The ingestion of these diuretics may also cause definite hypercalcemia in patients with primary or secondary hyperparathyroidism<sup>163,164</sup> and in those who have disorders causing increased bone resorption for example, Paget's disease, borderline vitamin D intoxication and juvenile osteoporosis.<sup>163,165</sup> Thiazides may stimulate the parathyroid glands, potentiate the action of PTH on skeleton, or act directly on the bone.<sup>161</sup> We have found that 200 mg of hydrochlorothiazide a day given for five days will cause or aggravate hypercalcemia in patients with primary hyperparathyroidism. Hypercalcemia appears on the second or third day and may persist or increase as long as the thiazides are taken. Although this procedure may also cause an elevation in the level of serum calcium (0.5 to 0.8 mg per 100 ml) in normal persons, hypercalcemia does not occur.

#### *Hypoparathyroidism and pseudohypoparathyroidism*

Hypoparathyroidism is a metabolic abnormality in which the secretion of PTH is not adequate.<sup>57,58,143</sup> The disease may be congenital, acquired or familial.<sup>166,167</sup> The acquired forms of this entity usually follow trauma to the parathyroid glands or their vascular supply or to the incidental removal of the gland during operation on the thyroid gland; and, on occasion, diminished functional parathyroid reserve may develop after I<sup>131</sup> treatment of thyrotoxicosis.<sup>168</sup> Hypoparathyroidism may be permanent or temporary and complete (no secretion of PTH) or incomplete (inadequate secretion of PTH).

The biochemical findings are those of varying degrees of hypocalcemia, hyperphosphatemia and low renal clearance of  $\text{PO}_4^-$  and high renal clearance of  $\text{Ca}^{++}$  in the presence of normal renal function (Charts 7 and 8). Parfitt demonstrated in humans that the magnitude of the hypocalcemia and the hyperphosphatemia is related to the degree of the hypoparathyroidism regardless of the cause of the hypoparathyroid state (Chart 27).<sup>169\*</sup> Most of the clinical manifestations of hypoparathyroidism are produced by the low concentration of  $\text{Ca}^{++}$  in the blood, and, therefore, the symptoms are those of increased neuromuscular excitability.

\* Also personal correspondence.

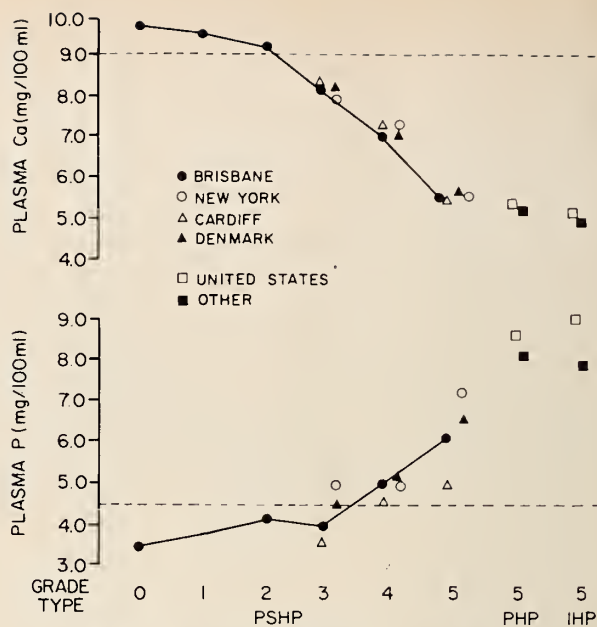


Chart 27.—The interrelationship of serum calcium and serum inorganic phosphate in the three forms of hypoparathyroidism, post-surgical (PSHP), idiopathic (IHP) and pseudohypoparathyroidism (PHP). (This data prepared by Dr. Michael Parfitt, Department of Medicine, University of Queensland, Brisbane, Australia, from personal studies and literature review.)

Hypoparathyroidism can be most accurately diagnosed by the measurement of the circulating level of PTH by a sensitive radioimmunoassay. These patients have low or no PTH in their blood despite the hypocalcemia.<sup>57,143</sup> These patients usually respond to the administration of parathyroid extract with a rise in the concentration of  $\text{Ca}^{++}$  in the plasma and with an increase in the renal clearance of  $\text{PO}_4^-$ . The degree of the hypoparathyroidism could be evaluated by assessing the response of these patients to a hypocalcemic stress produced by EDTA. In this test, the rate of return of plasma  $\text{Ca}^{++}$  concentration to the pre-EDTA level is considered a measure of the ability of the skeleton to mobilize calcium into the extracellular fluids; the greater the degree of hypoparathyroidism, the poorer is the response to the hypocalcemic stress (Chart 6).<sup>52</sup> The administration of a low calcium-high phosphorus diet may also help to diagnose patients with borderline or relative hypoparathyroid states; such patients, when placed on such a regimen, will develop definite hypocalcemia and a rise in the plasma concentration of  $\text{PO}_4^-$ , and the renal clearance of  $\text{PO}_4^-$  fails to increase appropriately.

Pseudo-hypoparathyroidism is a metabolic abnormality in which the skeleton and the kidney fail to respond to parathyroid hormone.<sup>92,113,166,170,171</sup> The disease may be congenital,<sup>166</sup> familial,<sup>170</sup> complete or incomplete. The biochemical findings and the response to acute or chronic hypocalcemic stress are identical to those seen in complete or incomplete hypoparathyroidism<sup>52</sup> (Charts 6 and 27). In these patients, the circulating levels of parathyroid hormone are normal or elevated,<sup>113,170,171</sup> and they usually do not respond to the administration of parathyroid extract. However, the end-organ refractoriness to the action of PTH in pseudo-hypoparathyroidism may vary from patient to patient. Usually there is little or no increase in  $\text{PO}_4^-$  clearance with acute or chronic administration of large doses of parathyroid extract or purified hormone;<sup>166,171,172</sup> in some cases the administration of comparable doses of the hormone may produce a moderate elevation in the concentration of the plasma  $\text{Ca}^{++}$  but rarely to a normal level. Recently, Suh et al,<sup>171</sup> studied a patient with pseudo-hypoparathyroidism in whom the kidney and the skeleton were totally unresponsive to parathyroid extract or purified hormones. This patient was then maintained normocalcemic with 100,000 International Units of vitamin  $\text{D}_2$  per day, and the subsequent administration of similar doses of PTH caused frank hypercalcemia, hypophosphatemia, and a pronounced rise in the renal clearance of  $\text{PO}_4^-$ . However, the correction of the hypocalcemia in this patient by parenteral administration of calcium did not increase  $\text{PO}_4^-$  nor did it affect the responsiveness of bone or kidney to PTH action. These investigators concluded that the administration of pharmacologic doses of vitamin D may alter the end-organ refractoriness to PTH.

In contrast to normal subjects, the administration of parathyroid extract to patients with pseudo-hypoparathyroidism does not cause an increase in the renal excretion of 3'5' cyclic-adenosinemonophosphate.<sup>92,172</sup> This defect may underlie the refractoriness of both the kidney and the skeleton to the action of PTH since the effect of the hormone on these end-organs may be mediated through this enzyme.<sup>89,92,172,173</sup> (See Table 3.)

The thyroid glands of patients with pseudo-hypoparathyroidism were found to contain large quantities of calcitonin,<sup>174</sup> and it was initially sug-

gested that hypocalcemia and resistance to PTH are due to increased secretion of calcitonin. However it has subsequently been shown that the high content of calcitonin in the thyroid glands was the consequence rather than the cause of the hypocalcemia.<sup>175</sup>

If we may define pseudo-hypoparathyroidism as a state of skeletal or renal refractoriness to the action of PTH, then a number of experimental and clinical situations may be considered to be "acquired pseudo-hypoparathyroidism"; these may include: (1) chronic renal failure, (2) vitamin D deficiency and vitamin D resistant states, (3) magnesium deficiency, and (4) administration of imidazole and related compounds.

At present, the preparation used most commonly for the treatment of hypoparathyroidism is vitamin  $\text{D}_2$  (ergocalciferol). Considerable care should be exercised in prescribing this drug, since pronounced hypercalciuria may develop when serum calcium approaches normal levels; and vitamin D intoxication may occur without changes in the dose of vitamin D or in the regimen of calcium supplementation. Therefore, it is important that serum calcium be monitored in such patients at relatively frequent intervals. Supplemental calcium is also useful in the management of hypoparathyroid states, but the relative low percentage of free calcium which is present in the available compounds should be kept in mind. In order to provide 1 gram of calcium, the patient must be able to take 8 grams of calcium lactate, 11 grams of calcium gluconate, 4 grams of calcium acetate, or 5.5 grams of hydrated calcium chloride.

Physicians involved in the care of these patients are well aware of the narrow range between the optimum therapeutic and the toxic doses of vitamin  $\text{D}_2$ . Ireland et al<sup>176</sup> carefully reviewed the histories of 30 hypoparathyroid patients treated for a total of 132 patient-years. The daily doses of vitamin D necessary to control hypocalcemia were in a narrower and lower ranges than generally thought. Poor results were seen in patients ingesting a mean of 1.73 mg or 68,200 IU per day, good or slightly suboptimal with a mean of 2.12 mg or about 82,000 IU per day, while hypercalcemia was frequent in patients receiving a mean of 3.28 mg or 131,000 IU per day.

Cholecalciferol (vitamin  $\text{D}_3$ ) and dihydrotachysterol are also available for use. The latter,



like ergocalciferol, is a product of irradiation of ergosterol (Chart 5). Dihydrotachysterol has fallen into some disrepute because of the variation in potency of A.T.10 (Hytakerol®), which was initially assumed to be dihydrotachysterol. However, A.T.10 was found to be a mixture of steroids, much less effective than crystalline dihydrotachysterol in controlling hypoparathyroidism.<sup>177</sup> Moreover, Harrison et al<sup>178</sup> found crystalline dihydrotachysterol to be 3 times more potent than vitamin D<sub>2</sub> in treating hypoparathyroidism; the toxic effects of this sterol disappear rapidly when the drug is discontinued. Dihydrotachysterol deserves wider use in the management of hypoparathyroidism. Recently, Kaye et al<sup>179</sup> reported that dihydrocalciferol is safer and more effective than vitamin D<sub>2</sub> in the treatment of renal osteodystrophy. Parfitt (personal communication) has summarized the physiological and pharmacological characteristics of vitamin D<sub>2</sub> and crystalline dihydrotachysterol (Table 4).

Pak and associates<sup>180</sup> have employed an active metabolite of vitamin D<sub>3</sub>, 25-hydroxycholecalciferol, in the management of vitamin D resistant rickets and have achieved some success with much smaller doses than those of vitamin D<sub>2</sub> or D<sub>3</sub> previously used without success. Further studies on this compound and other active metabolites of vitamin D<sub>3</sub> will be received with interest.

*Possible clinical states of an excess or deficiency of calcitonin, and its possible use as a therapeutic agent*

Since the discovery of calcitonin, there has been a search for syndromes with either excess or deficiency of this hormone as well as investigation into possible therapeutic uses of this agent. Medullary carcinoma of the thyroid, which arises from the parafollicular cells, and metastatic lesions from this tumor have been clearly shown to produce and secrete excessive quantities of calcitonin.<sup>182-186</sup> Despite high blood levels of calcitonin in such patients, hypocalcemia has only rarely been observed.<sup>182</sup> Several factors may explain the rarity of hypocalcemia: first, the syndrome occurs most commonly in adults who are resistant to action of the hormone; second, high circulating levels of parathyroid hormone have been found and such secondary hyperparathyroidism might prevent hy-

**TABLE 4.—Physiological and Pharmacological Characteristics of Vitamin D<sub>2</sub> and Crystalline Dihydrotachysterol (DHT)**

Action	Physiological D-Deficient		Pharmacological D-Replete	
	D <sub>2</sub>	DHT	D <sub>2</sub>	DHT
Ca absorption	++++	+	+	++
P resorption	—	—	+	++
Bone resorption	+	++	+	++
Osteoid maturation	++++	+	—	—
Mineral solubility	+	++	+	++

Clinical Comparison		
Characteristic	D <sub>2</sub>	DHT
Daily dose to prevent rickets	0.01-0.1 mg	1.0-2.0 mg
Daily dose in hypoparathyroidism	1.0-4.0 mg	0.25-1.0 mg
Time to reach maximum effect	2-6 weeks	1-2 weeks
Persistence after cessation	2-12 months	½-1 month

(Table made up from available data in the literature by Dr. Michael Parfitt, Department of Medicine, University of Queensland, School of Medicine, Brisbane, Australia.)

**TABLE 5.—Associated Clinical and Pathologic Syndromes in Patients with Sporadic and Familial Medullary Carcinoma of the Thyroid**

1. Diarrhea, possibly due to tumor secretion of prostaglandins.<sup>184</sup>
2. Cushing's syndrome due to ectopic production of ACTH.<sup>168</sup>
3. Pheochromocytoma, often familial and bilateral.<sup>184</sup>
4. Carcinoid or serotonin excess syndrome.<sup>188</sup>
5. Polypoid neuromas and ganglioneuromas of skin, lips, tongue, eyelids, gastrointestinal G.I. tract, bladder and bronchial tree.<sup>184</sup>

pocalcemia;<sup>182</sup> and finally, these tumors do not function autonomously—for example, the secretion of calcitonin may vary directly with the serum levels.<sup>182-186</sup> Medullary carcinoma of the thyroid either appears sporadically in middle age persons or later in life or occurs as a familial disorder in the first three decades.<sup>184</sup> The latter form is often associated with pheochromocytoma or multiple neuromas. This association is consistent with the unifying concept advanced by Pearse<sup>187</sup> that the parafollicular cells and those of the ultimobranchial bodies arose from neuroectodermal cells of the neural crest before their incorporation into the branchial pouches.

The clinical and pathological syndromes found in these patients are noted in Table 5.<sup>188</sup> Other than local symptoms, diarrhea which may be due to production of another hormonal agent, pos-

sibly serotonin or prostoglandin, and Cushing's syndrome due to secretion of ACTH by malignant parafollicular cells are the most common.<sup>184</sup> It is apparent that a diagnosis of medullary carcinoma of the thyroid can be made in a patient who has a mass in the neck by the finding of high levels of calcitonin in the blood.

Another disorder which was tentatively linked to excess production of calcitonin is osteopetrosis. This disorder is one wherein bone resorption fails to keep pace with bone formation; hence, there is excessive accumulation of mature bone. It is diagnosed roentgenographically by finding narrowing and poor differentiation of medullary cavities, thickening of the skull and narrowing of the sella tursica. The disorder is inherited in autosomal recessive manner in several species,<sup>189,190</sup> and in mice an increased rate of bone matrix formation, hypocalcemia, and parafollicular cell hyperplasia have been found.<sup>190</sup> It was suggested that the parafollicular cells were producing a factor, possibly calcitonin, which stimulated osteoblasts. Marks<sup>189</sup> was able to induce osteopetrosis in newborn mice by daily injections of parathyroid extract, in a manner previously reported by Selye;<sup>191</sup> mild hypercalcemia and parafollicular cell hyperplasia developed with the osteopetrosis. The latter did not develop if total thyroidectomy was performed before the experiment, and this led to the speculation that osteopetrosis might be due to chronic excesses of calcitonin. However, others<sup>192</sup> found that total thyroparathyroidectomy, which removes all calcitonin forming tissue in mice, did not prevent the osteopetrosis induced by parathyroid extract. Moreover, Gudmundson et al<sup>193</sup> found normal or low levels of calcitonin in three patients with osteopetrosis.

A clinical syndrome due to calcitonin deficiency has yet to be described in humans. Spontaneous hypercalcemia does not develop after total thyroidectomy in man; and changes in the plasma calcium concentration of these patients during and after a standardized calcium infusion differ very little from blood calcium levels of normal persons receiving the same calcium infusion.<sup>194</sup>

As both parathyroid hormone and calcitonin are present in the plasma of normal subjects, numerous investigators have suggested that idio-

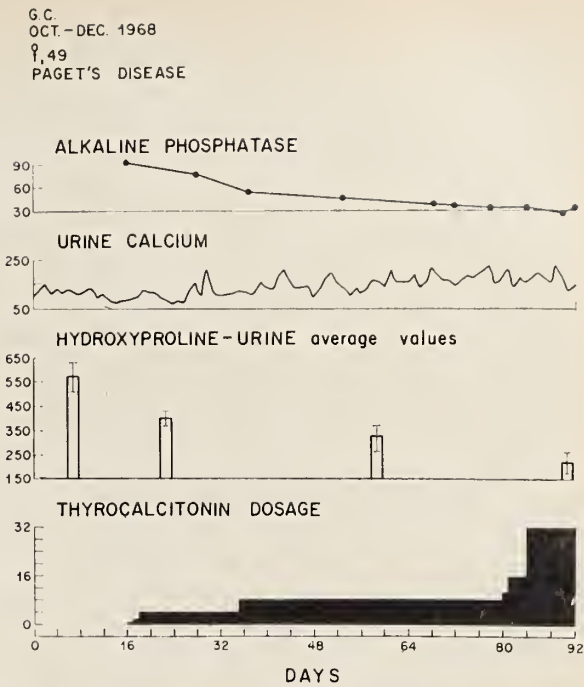


Chart 28.—Response to three months' intramuscular porcine calcitonin therapy in a patient with severe Paget's disease. Note the pronounced and progressive fall in serum alkaline phosphatase and urine hydroxyproline during therapy. There was also a consistent but slight rise in urine calcium.<sup>204</sup>

pathic osteoporosis may be due to a chronic imbalance between the circulating levels of these hormones. Unfortunately, no definitive data with respect to this problem are available. The metabolic and therapeutic effects of calcitonin in patients with idiopathic osteoporosis have been most conflicting.<sup>6,195-201</sup> In general, calcitonin seems to be of little therapeutic benefit; however, patients with idiopathic osteoporosis who have a greater-than-average rate of bone resorption may benefit from calcitonin. It is in these patients that acute administration of calcitonin may cause transient hypocalcemia and a decrease in the urinary excretion of hydroxyproline. Martin and Melick,<sup>195</sup> Bordier et al<sup>199</sup> and Bijovet et al<sup>201</sup> have suggested that this acute effect of calcitonin in patients with osteoporosis may help in the selection of patients likely to benefit from long-term therapy with calcitonin.

An important study of the osteoporosis accompanying thyrotoxicosis and its relation to possible deficiency of calcitonin has been carried out by Fraser et al.<sup>202</sup> They studied calcium metabolism and quantitatively measured bone density in treated and untreated thyrotoxic female patients



and in control normal subjects. In the untreated thyrotoxic patients, alkaline phosphatase, urinary calcium, and hydroxyproline to creatinine ratios in urine were all significantly higher and bone density less than in normal persons. After treatment with antithyroid drugs, bone metabolism and bone density returned to or toward normal; however, in the groups of patients treated with  $I^{131}$ , the abnormal bone density persisted. In addition, the latter group had prolonged hypercalcemia after calcium infusion.<sup>203</sup> These authors concluded that  $I^{131}$  therapy may destroy all the calcitonin-producing tissue, leading both to persistent abnormal bone resorption, despite euthyroidism, and to impaired homeostatic response to the intravenous calcium load. If this study can be extended to include measurements of circulating calcitonin levels and these are found to be a low, syndrome of calcitonin de-

ficiency would have been discovered in humans.

There has been great interest in the possibility that calcitonin would prove to have important therapeutic applications in various disease states in man.<sup>122</sup> The overwhelming evidence to date indicates that calcitonin has its greatest thera-

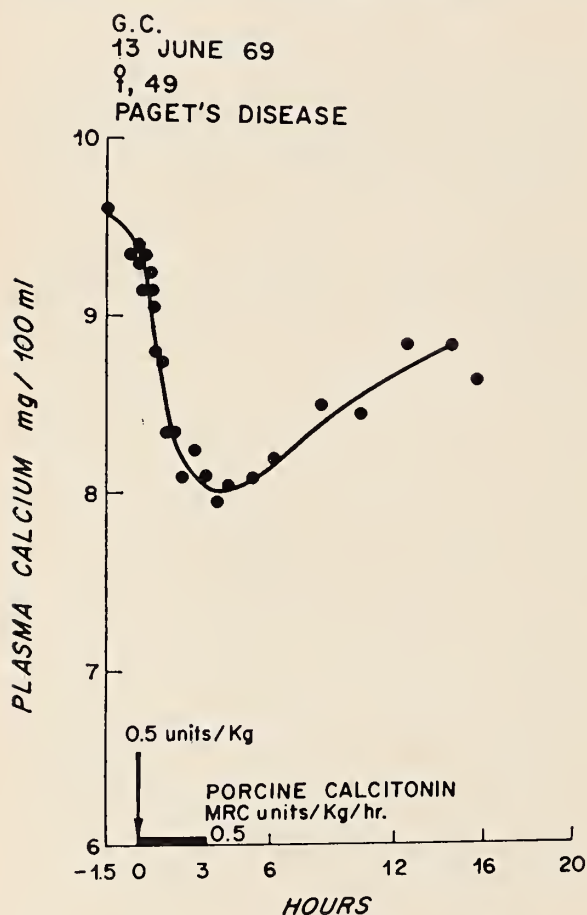


Chart 29.—Acute test of calcitonin responsiveness in a patient previously treated for five months with intramuscular porcine calcitonin. Note the continued sensitivity of this patient to intravenous porcine calcitonin despite prolonged treatment.<sup>204</sup>

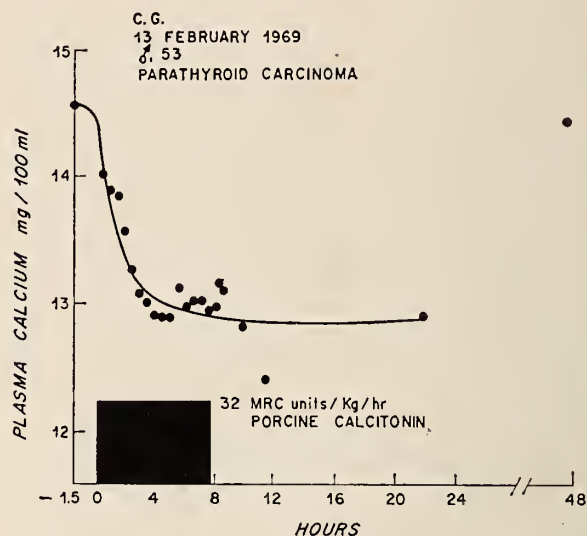


Chart 30.—Response of plasma calcium to massive dosage of intravenous porcine calcitonin (total dose 10,000 units over 8 hours) in a patient with chronic hypercalcemia due to functioning parathyroid carcinoma. The dosage infused was equivalent to 80 mg of pure porcine calcitonin.<sup>204</sup>

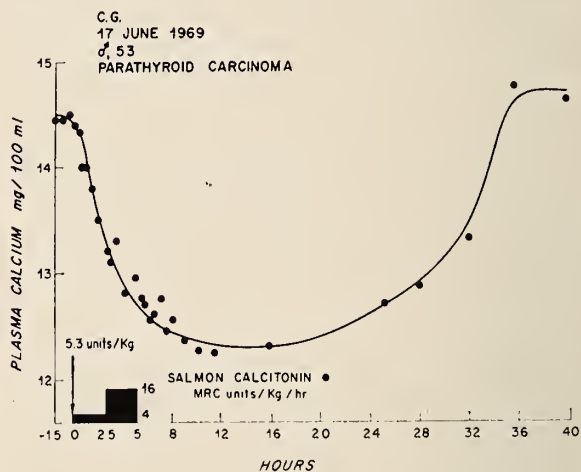


Chart 31.—Response of plasma calcium to salmon ultimobranchial calcitonin in the same patient as Chart 30. The total dose infused is equivalent to 0.6 mg pure salmon calcitonin. Note the equal or greater fall in plasma calcium despite the much smaller dose of peptide administered, as compared to Chart 30. Recovery of plasma calcium was still incomplete at 32 hours. Units were measured by assay in the rat against the MRC porcine standard, and the total dosage of salmon hormone was 2,200 units by this method.<sup>204</sup>

peutic effect in humans with disorders characterized by a decided increase in either osteoclastic or osteocytic bone resorption.<sup>6,196-201</sup> This would include almost all of the hypercalcemic syndromes and Paget's Disease, a normocalcemic disorder with a decidedly increased rate of bone resorption and turnover.<sup>6,196-201</sup> The responses to calcitonin in patients with these disorders are presented in Charts 28, 29, 30 and 31. The greater potency of salmon calcitonin relative to the purified porcine calcitonin is illustrated in Charts 30 and 31. Although large doses of calcitonin have been given acutely and chronically, there has been no development of antibodies, no significant toxicity and no tachyphylaxis.<sup>204</sup> While details of the clinical pharmacology, such as optimum dose, frequency of administration of the hormone, duration of activity and long-term effectiveness remain to be evaluated, these preliminary observations on the beneficial effect of calcitonin in states with increased bone resorption are encouraging.<sup>122</sup>

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## THE EFFECT OF "POT" ON PARENTS

"In certain adolescent subcultures, you will find that the normal teen-ager does experiment with 'grass' or marijuana, in a social and recreational context, on week-ends, at parties, in a very similar way, I suspect, to what the more assertive of us might have done with beer at age 16 during the time of prohibition, or with 'bathtub gin' for that matter. . . .

"Typically in New York City you might run into a 15-year-old from an upper-middle-class private school or some of the public schools, even the junior high schools now, who is in the social swing where there is tremendous pressure to do what the peer group does. They will take 'pot' occasionally. Most of the time you (as a physician) won't run into them. The only time you do is when they get into trouble over it. I consider these normal adolescents. . . .

"The most common presenting syndrome is alarmed, angry parents dragging in a child who has either been caught by them with some marijuana or has been 'busted by the fuzz'. . . . There have been dire threats of punishment. Parents frequently are terribly alarmed and angry and feel betrayed, and in this frame of mind may come in or be sent in for a psychiatric consultation.

"Here management depends largely on diagnosis. . . . I get a general survey of the ego strength of the adolescent, of how he is doing in the important areas of adolescent behavior: academically—how is he doing at school?, socially—does he have friends?, creatively—does he have some hobbies or outside interests? . . . If the adolescent scores pretty high on those points . . . , the management consists of just some brief counseling with the parents. I try to relieve their fears. I do direct magical reassurance that their child is not some kind of monstrous drug addict; I give them a good prognosis, which is absolutely true with these kids. Their prognosis is excellent. This decreases the parental fear which also tends to decrease their rage.

"Along with that the other thing I do is educate them in my own family standard of enforcement rather than discipline. I tell them that a certain amount of nonsense does not go in my house. I give them some anecdotes about what I've done with my own adolescents when they have displeased my square tastes. I try to give them some model of the old-time European family, which is terribly out of fashion but very useful. Adolescents need parents who can set standards and limits so they'll have something to rebel against."

—JESSE SCHOMER, M.D., New York City  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 15, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# Specialty Conferences

## Leukemia in Children

*Moderator:* MYRON KARON, M.D.

*Discussants:* DENMAN HAMMOND, M.D., CAROL B. HYMAN, M.D.,  
GERALD S. GILCHRIST, M.B.B.CH., AND GUSSIE HIGGINS, M.D.

*From the Division of Hematology, Childrens Hospital of Los Angeles  
and Department of Pediatrics, University of Southern California  
School of Medicine*

DR. KARON\*: Since the introduction of chemotherapy for acute lymphocytic leukemia, the median survival of children with this disease has increased six- to nine-fold.<sup>1</sup> This significant advance in survival has been due to the stepwise application of clinical and basic research knowledge developed in many centers and laboratories throughout the world. In spite of these impressive results, leukemia remains a fatal disease for which optimal treatment is unknown.

A child with leukemia presents a formidable challenge for developing means of improving cancer therapy. In the absence of curative therapy, the optimal management of this disease is synonymous with clinical research, since each new approach has the potential of being better than what has been done in the past. It is the purpose of this conference to sketch some of the empirical and theoretical bases for the therapeutic advances against this disease in an effort to emphasize those principles whose application

may lead to further improvements in management.

Dr. Hammond will discuss some of the salient features of childhood leukemia and indicate the scope of the cooperative clinical investigative effort now under way to improve the treatment of this disease.

DR. HAMMOND†: Cancer is responsible for more deaths among children than any other medical problem. Leukemia kills a greater number of children each year in the United States than did poliomyelitis during its worst epidemic year. Even though leukemia is relatively uncommon, having an incidence of only three cases per 100,000 population per year, no physician caring for children can afford to be ill-informed about the recent advances that have been made in therapy or unconcerned about the availability of adequate treatment facilities for his patients, since, increasingly the availability of such facilities has become one of the main determining factors in prognosis.

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Dr. Karon is a Leukemia Society of America Scholar.

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## Pathophysiology of Leukemia

Ninety-five percent of leukemia in children is acute; the only chronic types seen involve the granulocytic series. Approximately 80 percent of cases are classified on the basis of bone marrow cell morphology as either acute lymphocytic (lymphoblastic) or acute undifferentiated leukemia (ALL or AUL).

At the time of diagnosis, a bone marrow specimen from a child with acute leukemia usually demonstrates leukemic cells replacing over 90 percent of the hematopoietic elements. Because of bone marrow replacement, the patient has inadequate production of red cells, granulocytes and platelets, which lead to three well-known signs of the disease: anemia, infection, and hemorrhage. In addition to malignant cells in the bone marrow spaces, patients will often have accumulations of leukemic cells in enlarged peripheral lymph nodes, spleen, liver and kidneys.

The most common presenting symptoms of acute childhood leukemia include vague generalized aches and pains, easy fatigability, and anorexia—symptoms not unlike those of any childhood infectious disease. Once the diagnosis of leukemia is considered it can be established or eliminated by evaluation of the blood and bone marrow.

In the majority of cases, the hemoglobin will be below 8 grams per 100 ml and the platelet count will be less than 50 percent of normal. The leukocyte count may be normal, elevated, or decreased; but most patients will have leukemic cells representing about 50 percent of their peripheral leukocyte count. Some patients may have a perfectly normal blood count; others may manifest only a differential with a predominance of lymphocytes.

## The Effect of Chemotherapy on Survival

Before the introduction of chemotherapy, the median survival of children with acute lymphocytic leukemia was approximately three months from the time of diagnosis.<sup>1</sup> With the use of prednisone and methotrexate, the median survival was extended to approximately six months. After the introduction of 6-mercaptopurine in 1953 and the advent of antibiotics for treatment of infection, the median survival increased to approximately one year. During the following decade, there was little improvement in median

survival. Since 1963 the median survival has increased to two and a half years, and in several small series of patients treated by the most favorable regimens, the median survival has extended beyond three years.<sup>2</sup> Since the introduction of effective chemotherapy, a small number of patients, less than 5 percent, have survived five or more years from the time of diagnosis.<sup>3</sup> During the past decade, the proportion of long-term survivors has progressively increased. Some of these patients are free of disease 15 or more years from diagnosis.

Advances in the chemotherapy of leukemia have involved the discovery of new active agents as well as the development of better ways to use older agents. In addition, there have been significant improvements in supportive care, mainly in platelet replacement therapy and antibiotic management of infectious disease. Used early in the course of the disease, these techniques have kept some patients alive long enough to respond to specific chemotherapy who otherwise would have succumbed to hemorrhage or infection.

The increase in survival produced by chemotherapy is primarily the result of prolonged periods of drug-induced complete remission during which time the patient can enjoy good health and full activity. Because our strategy is not to admit the child to the hospital unless he needs care which cannot be obtained at home, the proportion of hospital time is usually quite small. Although the census of children under treatment for acute leukemia at the Childrens Hospital of Los Angeles averages approximately 110, the average in-patient census is only 5 (5 percent). Further analysis has indicated that only about 5 percent of a child's survival time is spent in the hospital. During most of their course, these patients are ambulatory. They attend school and carry on all their normal activities without restriction in any way.

One of the most important aspects of the care of the child in remission is his emotional well-being. The physician must be prepared to help the child and his family cope with the emotional and psychological hurdles that will characterize the course of the illness. An honest and trusting relationship must be established with the child appropriate for his level of understanding, and a healthy relationship must also be developed with the parents.

## Cooperative Clinical Investigation

Much of what is now known about effective chemotherapy of acute leukemia has been obtained as the result of a unique pattern of cooperation between the basic scientists in the general field of drug development and evaluation and clinical investigators in the field of oncology. The National Cancer Institute has sponsored, since 1955, a variety of programs of clinical cancer investigation for which purpose a number of nationwide cooperative groups were formed. Under the auspices of this program, more than 214,000 compounds were subjected to a variety of biological screening tests for anti-cancer activity between 1956 and 1964. From this group approximately 150 compounds were identified which, following extensive pre-clinical testing, appeared feasible to place into clinical study as potentially useful anti-cancer agents.

Clinical trials of such experimental anti-cancer chemotherapeutic agents have been divided into three phases. The objective of Phase I is the determination of the tolerated dose in humans and the varieties of toxic effects produced. Despite extensive pre-clinical pharmacologic and toxicologic experiments in animals, Phase I trials in humans are required to produce sufficient precise information with specific applicability to humans to determine whether the agent is safe for further human use. Phase II may not be sharply distinct from Phase I, but has as its prime objective the determination of the spectrum of anti-cancer activity of a compound, at optimally tolerated dose in humans. Compounds that emerge from Phase I and II clinical trials showing effective anti-cancer activity in clinical use may ultimately be subjected to Phase III trials in which the effectiveness of the newly developed agent is compared with more standard modes of therapy and is used in combinations with established therapies.

The development of new clinical therapies is highly dependent upon investigators with experience in clinical oncology and in clinical pharmacology and toxicology and with sufficient expertise to design and conduct valid and unbiased clinical trials. There are currently more than 20 cooperative groups sponsored by the National Cancer Institute for the conduct of collaborative clinical investigations involving various modes of therapy for human cancer. One of these, Chil-

drens Cancer Study Group A, restricts its clinical investigations to cancer in children, including the various types of leukemia and the more common solid tumors of childhood.

Childrens Cancer Study Group A is composed of 25 major pediatric institutions throughout the United States and Canada. At each institution there are chemotherapists, radiation therapists, surgeons and pathologists, all participating in collaborative clinical investigations in childhood cancer. The basic assumption justifying the existence of such groups is that by the combined efforts of multiple pediatric centers with interest and expertise in clinical cancer investigation in children, the resultant information derived from a large number of patients under study at once will prove more effective than the information that could be compiled by any single institution studying only the patients under its care.

The overall effectiveness of this program and its impact upon the advances in leukemia chemotherapy over the past 15 years has been well established. The single most favorable response rates both to single agents and to agents used in combination, including all agents now known to be effective against acute childhood leukemia, with the single exception of daunorubicin, have been achieved by cooperative group studies.

## Chemotherapy of Childhood Leukemia

DR. KARON: Advances in the therapeutics of childhood leukemia have occurred in overlapping stages. At first, single agents were used for both remission induction and remission maintenance. This approach soon gave way to use of multiple agents for both remission and induction and remission maintenance when it was discovered that compounds with independent modes of action and independent toxicity gave additive results.<sup>1</sup> Attempts were made to delay resistance by the use of drugs, either in sequence or cyclically. At about the same time, schedule dependence of methotrexate was demonstrated.<sup>5</sup> Kinetic studies in animal tumors indicated that cure of mouse leukemia was dependent on reducing the abnormal cell population to a single cell. This could be accomplished by using higher doses of drug for shorter periods. These findings greatly influenced the use of intensive chemotherapy in the clinic and gave impetus to a variety of clinical programs involving alterations of dosage and



TABLE 1.—*Remission Induction Acute Lymphocytic Leukemia*

AGENT(S)	RATE (%)	REFERENCE
Prednisone (Pred)	50-60	28
Vincristine (vcr)	50	29, 30, 6
Methotrexate (MTX)	30	31
6-mercaptopurine (6-MP)	30	32
Cytosan (Cyt)	25	33
L-Asparaginase (L-as)	50	8
MTX and 6-MP	30	31
Pred. and vcr	80-90	7
Pred. and 6-MP		34
Pred. and MTX		34
Pred. and Cyt		35

schedule. These therapeutic programs have been largely responsible for the increased survival of children with acute lymphocytic leukemia.

## Remission Induction

### *Acute Lymphocytic Leukemia*

The most useful agents for inducing remission in acute lymphocytic leukemia are listed in Table 1. Prednisone (Pred.) and vincristine (vcr) are drugs capable of inducing remission rapidly, almost always within four to six weeks. Prednisone has no significant bone marrow toxicity. Vincristine is rarely myelosuppressive, but its prolonged use has been associated with peripheral nerve palsies. Neurological complications can largely be avoided by the restriction of drug therapy to a four- to six-week period.<sup>6</sup>

Methotrexate (MTX), 6-mercaptopurine (6-MP), and cyclophosphamide (Cytosan®) produce a lower remission rate (Table 1). The use of these agents is associated with myelosuppression as evidenced by anemia, leukopenia and thrombocytopenia.

Combinations of Prednisone with vcr, 6-MP, MTX, or Cytosan have yielded remission rates of 80 to 90 percent with no increase in toxicity (Table 1). The absence of additive toxicity is due to the qualitative difference in the individual toxicity of these compounds. This difference permits the use of each drug at its optimal dosage. Combination of agents, which have qualitatively similar toxicity, such as 6-MP plus MTX, require a reduction in drug dosage usually by a factor of one-third.<sup>7</sup>

Recently a new drug, L-asparaginase, has been demonstrated to induce remission in 40 to 60 percent of patients in late stages of acute lymphocytic leukemia who have become unresponsive to other agents.<sup>8</sup> This is the first time an

TABLE 2.—*Remission Maintenance Acute Lymphocytic Leukemia*

AGENT(S)	MEDIAN DURATION (months)	REFERENCE
Prednisone	1.5	16
vcr	2.0	6
L-asparaginase	1.5	8
6-MP	8	16
6-MP and MTX (daily)	7	31
MTX (daily)	5-6	5
MTX (intermittent)	16	5
Cytosan	4-5	5

enzyme has shown activity against leukemia; consequently, a new approach to the management of the disease has been broached. L-asparaginase can cause severe toxic manifestations ranging from hepatitis to anaphylaxis. The ultimate role of this compound, as well as that of two other investigational drugs, cytosine arabinoside and daunorubicin, in the therapy of acute lymphocytic leukemia, is under intensive investigation.

### *Acute Myelocytic Leukemia*

Chemotherapy is less effective for the treatment of acute myelocytic leukemia (all subtypes included). Remission rates for children with this type of leukemia treated by standard means, such as with 6-MP, are less than 30 percent.<sup>9</sup> The use of newer agents and effective combination therapy has increased the remission rate to 40 to 50 percent. These programs include use of methylglyoxal-bis-guanylhydrazine (methyl-GAG),<sup>10</sup> daunorubicin,<sup>11</sup> and cytosine arabinoside<sup>12</sup> as well as the combinations cytosine arabinoside plus cyclophosphamide,<sup>2,13</sup> cytosine arabinoside plus thioguanine,<sup>14</sup> and POMP.<sup>15</sup>

## Remission Maintenance

### *Single Agent Treatment*

Armed with several ways of inducing remissions in 80 to 90 percent of patients with acute lymphocytic leukemia, chemotherapists have turned their major attention to ways of prolonging these remissions. This is of particular importance since the duration of survival of a child with acute leukemia is directly related to the duration of remission produced by therapy.<sup>1</sup>

The drugs commonly used for maintaining remissions are listed in Table 2. Vincristine, prednisone, and L-asparaginase are not particularly useful for maintaining remission, while 6-MP, methotrexate, and cyclophosphamide are. This

draws attention to the fact that there are some drugs which are uniquely effective for inducing remissions, while others are effective primarily for maintaining these remissions. Agents which maintain remissions tend to be more myelosuppressive than those which induce remissions.

Shortly after the unequivocal demonstration that maintenance therapy with 6-MP could prolong a prednisone-induced remission,<sup>16</sup> it became apparent that single agent maintenance programs with either 6-MP or methotrexate were capable of producing a median duration of remission on the order of six to eight months. The median duration of survival during this period was approximately one year.

### *Cyclic and Sequential Therapy*

In an effort to improve the duration of remission by delaying the development of drug resistance, the compounds in Table 2 were used sequentially or cyclically.<sup>17,18</sup> The usual approach was to induce remission with prednisone or vincristine, followed by maintenance with 6-MP. At the first relapse, the patient was retreated with the inducing agents to which he usually responded and then was maintained on methotrexate. This type of approach is termed sequential therapy. Cyclic therapy involves changing drugs during maintenance at fixed intervals, usually between six weeks and three months. These programs have resulted in a longer median duration of remission and a median survival of 18 to 24 months. Because this change in the median duration of survival occurred concomitantly with the introduction of additional anti-leukemic agents such as VCR and cyclophosphamide, the improvement in duration of remission may be more closely related to the availability of new active agents rather than a delay in the emergence of resistant clones.

### *Schedule Dependence*

Following the observations of Goldin,<sup>19</sup> in the mouse tumor L1210, that methotrexate given every four days was superior to daily treatment, a similar schedule was tried in man. The results indicated that intermittent MTX was three to five times more active than daily oral administration in prolonging remission.<sup>5</sup> Because of this important finding, similar studies were undertaken using 6-MP. The data to date indicates that 6-MP is not schedule-dependent.

### *Additive Therapy*

The duration of a 6-MP remission can be significantly prolonged if vincristine 1.5 mg per square meter of body surface is given monthly together with a five-day course of prednisone at 60 mg per square meter.<sup>20</sup> A similar prolongation of remission can be obtained with the additive use of daetomyein.<sup>21</sup> Although these findings have important implications for the design of an overall maintenance program, the optimal use of such agents, especially the latter, has yet to be established.

### *Intensive Therapy Early in Remission— The Influence of Cell Population Kinetics*

#### *Studies in Animal Systems*

The use of the mouse leukemia L1210 as a biological model has provided an important theoretical framework for several new chemotherapeutic approaches. The salient features of the L1210 model system can be summarized as follows:<sup>22</sup>

1. A single viable leukemia cell can proliferate to a number lethal to the host in  $15 \pm 0.5$  days, the time required to proliferate  $10^9$  cells. ( $2^n = 10^9$ ;  $n \log 2 = 9$ ;  $n = 30$  since the generation time is 0.5 days, then  $30 \times 0.5 = 15$  days).
2. The duration of survival of the animal after the inoculation of tumor is directly related to the number of tumor cells in the inoculum. Consequently, the duration of survival after a single antitumor treatment can be used to estimate the number of cells killed by a given treatment.
3. The same fraction of the total number of tumor cells is killed by a given dose of drug regardless of the number. The best way from the kinetic standpoint to eradicate tumor, therefore, is to deliver as much chemotherapy as can be tolerated by the host when the tumor is small.

There are some obvious analogies between the mouse model system and man. If chemotherapy is discontinued when the patient achieves a complete remission induced by either vincristine or prednisone, the disease will reappear rapidly; the average duration of the unmaintained remission being only two to three months. One explanation for this rapid recurrence is the regrowth of residual leukemic cells which were present at a concentration lower than that which could be detected by bone marrow examination. Histological examination of patients in hema-



tological remission has demonstrated persistent foci of leukemic cells.<sup>23</sup> One major objective of remission maintenance chemotherapy is the eradication of residual leukemic cells.

### *Studies in Man*

In November of 1962 a study given the abbreviated name VAMP (for vincristine, amethopterin, mercaptopurine and prednisone) was undertaken in an effort to reach this therapeutic objective.<sup>24</sup> The maximum tolerated dose of all four agents was given over a period of ten days to achieve remission. When the bone marrow had returned to normal, usually after two to four courses, additional ten-day courses of therapy, separated by an interval of ten to fourteen days to allow for recovery from toxicity, were administered. A median of five such treatments was given during remission, a procedure which has been termed "consolidation"; thereafter, therapy was discontinued. A similar program, termed BIKE, was undertaken involving the use of the same four agents, plus Cytosan, given consecutively in maximum tolerated doses immediately following a vincristine and prednisone-induced remission.

Twenty of the 23 patients who completed the consolidation treatment in the VAMP and BIKE programs after the achievement of complete hematological remission had recurrent leukemia within 35 weeks of the time therapy was stopped. For most of the patients, therefore, eradication of the disease was not accomplished. The long duration of unmaintained remission, however, did indicate that the amount of residual leukemia was reduced significantly by consolidation therapy.

The effectiveness of consolidation programs of intensive multiple agent therapy in prolonging unmaintained remission, and thus presumably reducing the total body burden of leukemia cells, prompted the use of intermittent intensive chemotherapy over a longer period. One such program, termed POMP, was developed at the National Cancer Institute.<sup>25</sup> This program consisted of a similar induction and consolidation program, followed by monthly courses of prednisone, vincristine, methotrexate, and 6-MP. This approach has succeeded in increasing the median duration of survival of children with acute lymphocytic leukemia to three years.

Another program, based on similar biological considerations, which has also increased the median survival beyond three years, has been de-

veloped by Acute Leukemia Cooperative Group B.<sup>26</sup> This program consists of a vincristine and prednisone induction phase, followed by methotrexate 15 mg per square meter per day for five days, twice a month, for a period of eight months. In addition, some patients have received prednisone and vincristine for five-day courses each month. Following the initial eight months of intensive methotrexate treatment, patients are given methotrexate by mouth, 30 mg per square meter twice weekly. The maintenance phase of this program has produced remissions which have lasted for a median of 25 months. Eighty percent of the patients were still living at that time; consequently, the median duration of survival will probably exceed three years.

### *Future Directions for Therapeutic Research*

#### *Chemotherapy*

Advances in chemotherapy will continue to be made by the development of newer leukemic agents and by exploring better ways of using those currently available. In developing such programs, many of the concepts derived from animal model systems concerning cell population kinetics, optimal dosage and schedule information, and pharmacological data will be utilized. Such programs have as their theoretical core the concept that leukemia is the result of an abnormal clone of cells which must be eradicated to produce cure.

#### *Immunotherapy*

Mathé in a pioneering study has presented evidence in a small group of patients that weekly injection of BCG may prolong remission.<sup>27</sup> Presumably BCG acts by a non-specific stimulation of the reticuloendothelial system. A controlled clinical trial of the efficacy of BCG is currently under way in the United States under the auspices of the Childrens Cancer Study Group A.

In addition to the use of non-specific immunotherapy, the potential for utilizing antigenic determinants specific for the leukemic process is under intensive investigation. These studies are prompted by the findings in animal tumors of tumor-specific transplantation antigens (TSTA) on the surface of tumor cells. Such antigens can elicit a weak host response (cellular immunity) which can, in some instances, be exploited to

therapeutic advantage. The evidence that such tumor-specific antigens exist on the surface of leukemia cells is only fragmentary.

### *Bone Marrow Transplantation*

The possibility that the graft vs. host (GVH) reaction observed when allogeneic (between individuals of the same species) bone marrow transplantation is performed can be utilized to eradicate leukemia is under intensive investigation. So far such procedures have not been successful and have been complicated by fatal GVH reactions, septic deaths, rapid recurrence of leukemia, and graft rejection.

### *The Complications of Leukemia*

DR. HYMAN\*: There are two principal problems which frequently complicate the course of children with leukemia. These are the occurrence of contagious diseases of childhood and extramedullary involvement by leukemia, especially of the central nervous system and the testes.

#### *Contagious Diseases*

Children with leukemia may not handle virus diseases as well as normal children. Although rubella and mumps are usually mild, prolonged severe disease and fatalities have occurred with rubeola, varicella, and herpes zoster.<sup>37,38</sup> There is no single explanation for the reduced resistance and poor handling of these infections in children with leukemia. Both the disease, especially during periods of relapse,<sup>39</sup> and the therapy, steroids and immunosuppressive agents, contribute.

#### *Immunization*

Immunization with live virus vaccines is contraindicated in patients with leukemia, as it may lead to generalized disease. The live virus vaccines include those against mumps, rubella, rubeola, poliomyelitis (Sabin vaccine) and smallpox. On the other hand, immunization with DPT or the Salk poliomyelitis vaccine is safe.

For an exposed child, management should be directed toward disease prevention. If the exposure has been recent enough for human immune globulin to be of value, it should be given without delay and in sufficient dose to prevent rather than modify the disease.

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Management of the virus disease when present is aimed at minimizing its severity and preventing secondary infections.<sup>40</sup> Handling of steroid therapy is controversial, as steroids are known to impair host response to virus infections and may enhance virus multiplication.

In determining whether to modify or discontinue steroid therapy, each case must be appraised individually, taking into consideration the status of the leukemia, the antileukemic therapy, and the clinical condition of the patient. We generally continue prednisone therapy in full dose when the risk of leukemia deterioration poses a greater hazard than the virus disease. On the other hand, it is preferable to decrease the dose to physiologic levels or discontinue it whenever the status of the leukemia permits.

Since most antileukemia agents are both immunosuppressive and myelosuppressive, ideally they should be discontinued when the child is known to have been exposed to a contagious disease or when such a disease develops. For a child in remission or one who has leukopenia secondary to drug toxicity, the decision to stop the drug is easy. However, for a child in partial or complete relapse, there are individual modifying circumstances to consider: Can the virus disease be prevented in this child with passive immunization? Is the leukemia in sufficient control to permit temporary withdrawal of the drug? Which is the greater risk?

#### *Extramedullary Disease*

Aside from the reticuloendothelial system, leukemia is most commonly found in the central nervous system and testes. The frequency of leukemia infiltration of these two anatomic sites is believed to result from the inability of antileukemic agents, given in clinically feasible dosages, to reach them from the blood stream. These two areas are considered to be pharmacologically protected.

#### *Central Nervous System Leukemia*

Increased cerebral spinal fluid (CSF) pressure is the most common manifestation of meningeal leukemia.<sup>41</sup> If symptoms such as headaches or vomiting are present the diagnosis is simple; however, in some children the increased CSF pressure may first be discovered by finding papilledema on routine funduscopic examination. These children



should be treated since meningeal leukemia can result in seizures, blindness, and the sudden onset of coma.

Abnormal weight gain is another frequent sign of CNS disease. The child may continue to gain weight when steroids are discontinued or may be unable to fit into his clothes, or the physician may note an unusual steady increase in weight with no other explanation. Since in these cases the leukemic infiltrate is in the region of the hypothalamus, not the meninges, the CSF may or may not be abnormal. Some of these children have been treated for CNS disease despite normal CSF findings, and have responded.

When methotrexate is instilled into the CSF, the drug reaches the meninges and superficial areas, rather than the deeper portions of the brain. For this reason, the drug is the treatment of choice for meningeal leukemia and is less effective for treatment of deep lesions.<sup>42</sup> In previous studies we have shown that methotrexate will only affect CNS disease in those patients whose systemic disease responded to the drug the first time it was given; that is, their leukemia cells were initially methotrexate-sensitive. In such patients, meningeal leukemia will respond to the drug. Should the systemic disease become methotrexate-resistant, the leukemia cells in the meninges may still be methotrexate-sensitive. This is because resistance to methotrexate is dose-related and the dose per unit volume in the CSF is high. The development of systemic resistance therefore is not a contraindication to intrathecal therapy.

A course of intrathecal methotrexate consists of 0.4 mg per kilogram per dose (12 mg per square meter) based on the presteroid or basic weight of the patient, on two separate days with one day intervening. We usually recheck the spinal fluid after one week. If symptoms persist or the CSF is still abnormal, another one or two injections of methotrexate may be necessary. Symptomatic relief may be immediate after the first spinal tap or may take as long as ten days to be evident. Unfortunately, meningeal leukemia will usually recur in six weeks to three months. Repeat courses may be given. Systemic methotrexate therapy should be omitted during intrathecal therapy.

X-radiation is the treatment of choice for meningeal leukemia in children whose systemic disease was initially methotrexate-resistant and also

in those whose CNS lesion is in the brain substance. Because conventional therapy using 1,000 rads is inadequate for control of CNS disease, our radiotherapist recommends 2,000 rads to the head and spinal axis. With this dose, he has achieved considerably longer duration of remission. The 2,000 rads dose can be repeated twice.

### *Testicular Infiltration*

Frequently it is not appreciated that infiltration of the testes is one of the most common complications of acute leukemia in male children.<sup>43</sup> Most commonly the testicular enlargement is unilateral and produces minimal discomfort. However, in patients with unilateral enlargement, who have had needle biopsy of the contralateral "normal" testicle, leukemic infiltrations have been found. Because the testes are a pharmacologically protected area, radiation therapy bilaterally is the treatment of choice.

Psychologic preparation before radiation, with reassurance of a lack of impairment of secondary sex development, is most important.

### *Platelet Replacement Therapy*

DR. GILCHRIST\*: Thrombocytopenia is invariably seen at some time during the course of acute leukemia in childhood. This is most often the result of bone marrow infiltration by leukemic cells, but with the use of various forms of intensive chemotherapy a low platelet count can also be a life-threatening complication of drug-induced marrow aplasia. Before the introduction of platelet transfusion on a relatively large scale in a number of centers in the United States, hemorrhage was the major single cause of death in patients with acute leukemia. These centers now report a striking decrease in the percentage of patients dying of hemorrhage.<sup>44,45</sup> At the Childrens Hospital of Los Angeles, for example, hemorrhage is now considered to play a major role as a cause of death in fewer than 20 percent of patients with acute leukemia, an incidence similar to that observed at the Roswell Park Memorial Institute.<sup>44</sup> The provision of platelets for transfusion has not only altered the course of the disease in its terminal phases, but of particular importance has been the prevention of fatal hemorrhagic complications during the period of

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TABLE 3.—*Effect of Hemorrhage, Temperature and Sepsis on Response to Platelet Transfusion*

OBSERVATION	NO HEMORRHAGE OR SEPSIS		ACTIVE HEMORRHAGE					
			NO SEPSIS			PROVEN SEPSIS		
Temperature (°C)	<39	<38	38-39	39-40	>40	38-39	39-40	>40
Mean Platelet Increment ( $\times 10^3$ )/m <sup>2</sup> /unit Infused	18	13.4	13.3	8.3	7.9	10.2	4.0	1.5

induction of remission, thus allowing larger numbers of children the benefit of consolidation and maintenance chemotherapy.

Platelets can be administered to the thrombocytopenic patient in the form of fresh whole blood, platelet-rich plasma, or platelet concentrate. In the pediatric population the use of whole blood or platelet-rich plasma is limited by the volume of material which would have to be administered in order to obtain satisfactory increments in platelet count. Utilizing reasonably simple techniques which are well within the capability of virtually all blood banks, most of the platelets from a unit of whole blood can be concentrated in a much smaller volume, thus allowing for rapid infusion of large numbers of platelets without fear of circulatory overload. These platelet concentrates can be produced as a by-product of routine blood banking and the platelet-poor plasma and red cells reconstituted or stored as separate components.

The development of plasmapheresis techniques has vastly improved the efficiency of platelet procurement since, by returning the red cells to the donor, platelets from two or more units of blood can be collected at a single bleeding and this process can be repeated twice weekly when necessary.<sup>46,47</sup> Each healthy donor therefore has the potential of providing 40 or more units of platelet concentrate in a 12-week period as compared with only two units if whole blood is donated.

Methods for platelet procurement and donor qualifications have recently been summarized by a committee of the Acute Leukemia Task Force of the National Cancer Institute.<sup>48</sup> Current American Association of Blood Banks standards do not allow for prolonged storage of platelet concentrates and, because of this, concentrates should be administered within six hours of donation.

Each unit of platelet concentrate obtained

from 500 ml of normal whole blood contains an average of  $10^{11}$  platelets. Following infusion of platelet concentrate, we have observed a median increment in platelet count of 12,000 per cu mm for every  $10^{11}$  platelets infused per square meter of body surface. This represents a 30 to 40 percent yield when one calculates the response which could be anticipated assuming full recovery of donor platelets. Obviously the procedures necessary to produce platelet concentrates contribute to losses, both in numbers and viability. It should be noted that the response to platelet transfusions is extremely variable. Some patients show no evidence of circulation of infused platelets even after extremely large doses.

Most platelet concentrates contain small numbers of red cells. Patients should receive platelets from donors who are compatible with respect to ABO and Rh red cell antigens, wherever feasible.

Information is accumulating on the role of platelet antigens and antibodies in influencing the response to platelet transfusions.<sup>49</sup> Recent work indicates that histocompatibility antigens are found on platelets as well as leukocytes. Successful infusions of HL-A compatible platelets have been reported in patients who were completely resistant to infusion of platelets from HL-A incompatible donors.<sup>50</sup> Fortunately, development of platelet antibodies and resistance to platelet infusions is a relatively uncommon finding in patients with acute leukemia, presumably because they are receiving intensive immunosuppressive therapy. This is in contrast to patients with aplastic anemia who commonly exhibit a poor response to platelet replacement therapy after only a few infusions and in whom platelet antibodies have been identified.<sup>51</sup>

The presence of gross hemorrhage with or without septicemia will significantly modify the response to platelet transfusions. Table 3 summarizes some data from the Childrens Hospital



of Los Angeles. All patients had platelet counts below 20,000 per cu mm before infusion. Even in the absence of proven septicemia, febrile patients respond less well than those without an elevated temperature. Naturally, patients with a large spleen may manifest a hypersplenic picture and in those circumstances infused platelets would not be expected to circulate if they are trapped in the enlarged spleen.

In our experience, a dose of 6 units of platelet concentrate (i.e., the platelets derived from six 500 ml units of whole blood) per square meter of body surface can be expected to produce a rise in platelet count above 25,000 in almost every patient. This level is adequate for the prevention of spontaneous hemorrhage, hence this dosage schedule can be expected to produce hemostasis even though from patient to patient it might be impossible to anticipate the exact response. It is most helpful, however, in predicting future responses to routinely perform a platelet count before an infusion and again one hour after its completion. This one-hour post-transfusion count gives an excellent indication of the efficacy of the infusion but careful clinical observation is of the greatest importance since sometimes clinical hemostasis is achieved even when there is a minimal rise in platelet count. The opposite is also true, in that some patients continue to bleed in spite of more than adequate numbers of circulating platelets. Under these conditions, a careful search must be undertaken for causes of bleeding other than thrombocytopenia. These might include gastrointestinal ulceration, hemorrhagic cystitis, liver disease, or disseminated intravascular coagulation which is a most serious complication particularly of monomyelocytic leukemia. In such circumstances platelets may not only be expected to provide no hemostatic effect but in patients with intravascular coagulation, who have not had anticoagulation therapy, platelet transfusion might aggravate the situation by providing more substrate for intravascular clotting.

A platelet count obtained the morning following the transfusion will provide information on the survival of the infused platelets and indicate when further transfusions may be necessary. In most situations adequate platelet levels can be maintained by infusions of six units of platelet concentrate per square meter of body surface on alternate days. In our experience 40 to 60 percent

TABLE 4.—“High-Risk” Patients

- 1) PLATELET COUNT 10,000/mm<sup>3</sup>
- 2) ACUTE MONOMYELOCYTIC LEUKEMIA
- 3) HIGH LEUKOCYTE COUNT
- 4) INFECTION
- 5) INTENSIVE CHEMOTHERAPY

of the initial increment is still in circulation 24 hours after infusion. For practical purposes a program allowing for infusions on Mondays, Wednesdays and Fridays will eliminate the need for emergency bleeding of donors at night and on the weekends. Once again, it should be stressed that each patient's needs must be determined individually.

Although in general when the platelet count is below 10,000 cu mm the risk of hemorrhage is extremely high, it is well recognized that many patients may have no significant bleeding in spite of extremely low platelet counts. A particularly high-risk group of children can, however, be identified (Table 4). The incidence of fatal intracranial hemorrhage is probably highest in children with acute myelomonocytic leukemia and in patients with extremely high white blood cell counts irrespective of the cell type. Such patients may have fatal intracerebral hemorrhage even though the platelet count is over 50,000, as the result of leukostasis and rupture of cerebral vessels.<sup>52</sup> Patients with infection also have a greater tendency to bleed and their response to platelet transfusion is usually suboptimal.

It is apparent, therefore, that one cannot always predict the needs of a particular patient with respect to platelet transfusions and this problem is compounded by the relatively short survival time of the infused cells in the circulation. The development of suitable means for preserving and storing platelets will assure the clinician that platelets would be available at any time should any change in the patient's condition warrant their infusion. This would also permit bleeding of donors on a regular basis and storage of fresh platelets not needed on that particular day for later use in emergency situations. Such a system would also allow for centralized production of platelets and shipment to smaller centers where facilities for platelet procurement and preservation might be limited.

A number of techniques for platelet preservation have been investigated. Murphy and asso-

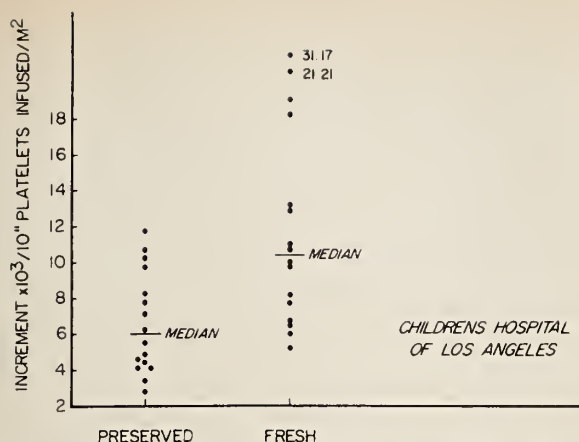


Chart 1.—Platelet recovery following paired infusions of fresh and DMSO-cryopreserved platelet concentrates.

ciates<sup>53</sup> have recently shown that infusion of platelet-rich plasma and platelet concentrate stored at room temperature for up to 72 hours resulted in significant in vivo recovery and survival after <sup>51</sup>-C<sub>2</sub> labeling. This short-term storage, if proven safe and efficacious in larger studies, would relieve blood banks and clinicians of a major limiting factor in platelet procurement and supply.

Another approach to the problem has involved cryopreservation utilizing either glycerol<sup>54</sup> or dimethyl sulfoxide as a preservative. As part of a project sponsored by the Acute Leukemia Task Force of the National Cancer Institute, 200 units of platelets procured and frozen in 5 percent dimethylsulfoxide and 5 percent dextrose<sup>55</sup> were shipped in liquid nitrogen from Philadelphia to Los Angeles where their clinical effectiveness was studied. Maximum increments in platelet count following infusion of these platelets preserved by freezing are summarized in Chart 1. Results were compared with those from infusions of fresh platelets given to the same patients within two days, either before or after administration of the preserved product. In order to reduce the number of variables, these studies were undertaken on thrombocytopenic patients in whom there was no evidence of sepsis or major hemorrhage. No major side effects were noted and we are encouraged by the results, since even a 50 percent yield from a preserved product would significantly improve the efficiency of platelet procurement and transfusion program by making platelets available for transfusion in emergency situations without resorting to emergency blood donation.

## Granulocyte Replacement Therapy

DR. HIGGINS\*: A major limitation of chemotherapy of acute leukemia has been the development of bone marrow failure with resultant anemia, thrombocytopenia and granulocytopenia.<sup>45</sup> Anemia can be corrected easily with red cell transfusions, and hemorrhage usually can be controlled by adequate platelet replacement through the use of platelet transfusions as indicated by Dr. Gilchrist. In an attempt to avoid the increased susceptibility to fatal bacterial infection associated with granulocytopenia, chemotherapy must often be restricted even in the face of progressive leukemia.<sup>56</sup>

Replacement therapy with granulocytes would be a rational form of supportive care. The transfusion of granulocytes from patients with chronic myelogenous leukemia into leukopenic recipients can raise the level of circulating leukocytes significantly when a dose of 10<sup>11</sup> granulocytes per square meter is used.<sup>57</sup> This rise in circulating granulocytes is associated with beneficial responses to Gram-negative infections.<sup>57</sup> Such a source of granulocytes presents at least two obvious problems: One is that a group of patients with chronic myelogenous leukemia who would be suitable as donors must be constantly at hand—a most unique circumstance; and the other is that one would prefer to avoid infusion of malignant cells into some patients who may have the potential for either long-term remission or cure. Consequently, attention has been turned to procuring granulocytes from normal persons.

In contrast to platelets, which are easy to obtain by plasmapheresis, the relatively small number of granulocytes in normal blood and the difficulty in separating granulocytes from red cells have made the routine use of this form of therapy impractical. To obtain sufficient granulocytes from normal blood for an adequate white cell transfusion—that is, 10<sup>11</sup> granulocytes—40 units of whole blood would be needed.

The National Cancer Institute in collaboration with the IBM Corporation has developed a blood separator designed to continuously remove white cells from the circulation of a donor while returning other components such as red cells and platelets.<sup>58,59</sup> Because of the large reserves of granulocytes in normal persons and the rapidity with

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which these reserves can be replenished, the use of this approach has been shown to be completely safe for the donor.<sup>60</sup>

There are several obstacles to the routine use of this apparatus for granulocyte procurement. Under the best conditions, the maximum yield from a normal donor has been in the range of  $1 \times 10^{10}$  to  $5 \times 10^{10}$  cells. This number of granulocytes is not sufficient to raise the white count significantly in a leukopenic patient. The majority of leukopenic patients will have been exposed to blood products and consequently will have circulating leukoagglutinins (leukocyte antibodies). Those few patients who have not developed leukoagglutinins before white cell transfusion will develop them shortly thereafter. Thus far, recipients with circulating leukoagglutinins have not responded to white cell transfusions. Unfortunately, without a reproducible means of increasing the yield of granulocytes to the range of  $10^{11}$  cells, there is no way to test whether the presence of leukoagglutinins or insufficient leukocyte dosage is the reason for the poor response.

There are three approaches to this problem: (1) increase the donor yield; (2) use HL-A compatible donors; (3) attempt to prevent sensitization by immunosuppressive agents. Only the first approach holds any promise of practicality in children, since the likelihood of an HL-A compatible sibling old enough to undergo leukopheresis is small and most patients are already on immunosuppressants, yet leukoagglutinins have developed. Ways of increasing the yield of donor white cells is under intensive investigation.

## Summary

Leukemia is the most common fatal disease of children between the ages of one and fifteen years. Within the past several years major advances in specific therapy and supportive care have led to significantly longer survival time. In large measure, this progress has been due to the development of a greater variety of antileukemia drugs and improved schedules for their use. Such developments have been the result of cooperative efforts among a variety of institutions with specialized facilities and personnel to deal with this serious multifaceted problem. Treatment is a highly special problem in which careful individual adjustments and selections of mode are of pressing importance.

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## THE "INDIRECT HERNIA"

"One possible cause of late hernia recurrences might be overlooking an indirect sac at the time a direct hernia is repaired. Frequently the surgeon is so enthusiastic over his discovery of the direct hernia and his reconstruction of the problem that he does not skeletonize the cord at the internal ring and look for a small indirect sac. If that sac is left, then in later years it may well develop into a so-called recurrence. I've been guilty of this myself. In every direct hernia, before you start the repair, you should take a very careful look at the proximal portion of the cord to be sure that an indirect hernia is not present."

—FRANCIS C. USHER, M.D., Houston

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## MEDICAL STAFF CONFERENCE

# Medical Management of Chronic Renal Disease

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SLEISENGER: \* Dr. Robert Schrier† will discuss the important clinical topic of medical management of chronic renal failure.

DR. SCHRIER: † The advent of renal transplantation and chronic dialysis has revolutionized the treatment of end-stage renal disease. Nevertheless, medical management remains the primary treatment of most patients with chronic renal failure. Furthermore, patients treated with chronic dialysis or renal transplantation still require a substantial degree of medical management.

### Reversible Factors in Chronic Renal Disease

One of the most important aspects of the medical management of the patient with chronic renal failure is a thorough search for reversible factors which may have worsened the patient's already limited renal function. Chart 1 shows the geometric relationship between renal function, creatinine and blood urea nitrogen concentration (BUN). This chart illustrates that on a normal protein intake urea and creatinine clearances may decrease to a level 50 percent below normal with only a very slight increase in BUN and serum creatinine concentration. However, if the initial urea and creatinine clearances are 25 percent of nor-

mal, a slight further decrease in the renal clearance of these substances will greatly increase the BUN and serum creatinine concentration. In this circumstance, the loss of literally a few functioning nephrons may convert a well-compensated patient with chronic renal disease to a severely uremic patient. Conversely, the recognition and

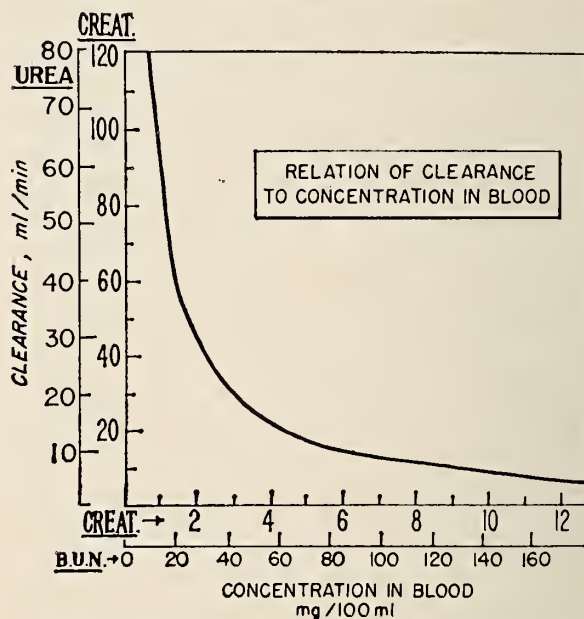


Chart 1.—Rapid rise in blood creatinine concentration and BUN after their renal clearance has diminished to levels greater than 50 percent below normal. Reproduced with permission of publisher.<sup>1</sup>

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**Table 1.—Reversible Factors in Chronic Renal Disease**

Urinary Tract Infection	Pericardial Tamponade
Urinary Tract Obstruction	Accelerated Hypertension
Volume Depletion	Electrolyte Disturbances
Congestive Failure	Acute Renal Failure

treatment of reversible factors may produce an equally dramatic improvement in the patient's clinical state in association with a very small increase in glomerular filtration rate (GFR).

The natural history of the renal disease is a primary consideration when searching for reversible factors. For example, in the absence of complicating factors, gradual deterioration of renal function in chronic glomerulonephritis or chronic pyelonephritis occurs over a period of months or years. Deterioration over a period of days or weeks therefore suggests that a potentially reversible factor or factors may have intervened and been responsible for the patient's clinical deterioration. Some of the potentially reversible factors which may worsen the clinical state of a patient with chronic renal disease are shown in Table 1. The detection and treatment of urinary tract infection may arrest or prevent progression of chronic renal failure. Damaged kidneys, whether damaged by congenital abnormalities or disease, seem more prone to infection than structurally normal kidneys; hence, instrumentation or catheterization is best avoided in patients with chronic renal disease. Many urinary tract infections may be asymptomatic or the patient too uremic to allow elucidation of the symptoms; therefore, urine cultures should be a routine procedure in the work-up of patients with chronic renal failure, particularly those with a rapid deteriorating clinical course.

Urinary tract obstruction is a factor to consider in any case of chronic renal disease with rapid clinical deterioration. However, only when conditions strongly suggest it should retrograde pyelography or instrumentation be performed, since, in general, high dose or constant infusion intravenous pyelography is sufficient to exclude obstruction. The most common cause of obstruction is benign prostatic hypertrophy. Suprapubic percussion, postvoid films after intravenous urography, and cystourethrography following suprapubic instillation of contrast material will be sufficient for evaluation of obstruction without instrumentation in patients with chronic renal disease. Since some patients with chronic renal dis-

ease may have only one remaining functioning kidney, acute partial or complete obstruction of the remaining kidney may be associated with rapid deterioration. A plain film of the abdomen should always be obtained to exclude the presence of radiopaque calculi. Such a film, with tomography, will also allow evaluation of the kidney size in patients with renal failure. If the kidneys are of normal size, the process causing the renal failure may be acute and thus totally, or at least partially, reversible. However, it should be emphasized that the size may be normal even in end-stage, irreversible renal failure associated with amyloidosis, diabetic glomerulosclerosis and scleroderma, or in rapidly progressive glomerulonephritis.

Depletion of the extracellular fluid volume is probably the most common of the factors which may cause rapid deterioration of renal function. For example, gastroenteritis with nausea, vomiting and diarrhea and an associated decrease in intravascular volume may develop in a patient with compensated chronic renal disease. The decrease in intravascular volume may in turn diminish renal perfusion and GFR and thereby cause a rapid rise in BUN. A vicious cycle may then ensue in which the nausea and vomiting of uremia produce further volume depletion and diminution in renal function. In evaluating a patient with chronic disease a thorough history and physical examination should therefore be obtained in an effort to find out whether volume depletion may be a cause of the decline in clinical state of the patient. The administration of tetracycline may also increase the BUN by inhibiting the rate of anabolism, and the progressive azotemia may in turn initiate a vicious cycle of vomiting, volume depletion and further azotemia.<sup>2</sup> Although a direct nephrotoxic effect of the tetracyclines remains to be established, certain antibiotics, such as kanamycin and colistimethate, may be associated with increased azotemia due to a direct nephrotoxic effect.<sup>3</sup>

Congestive heart failure is another "prerenal" factor which may lead to rapid deterioration of renal disease. Several varieties of congestive heart failure may occur in association with chronic renal disease. However, arteriosclerotic and hypertensive cardiovascular disease and so-called uremic cardiomyopathy are the most common forms. Uremic cardiomyopathy is an ill-defined form of heart disease which has been described in patients with advanced chronic renal failure.<sup>4,5</sup> Severe



cardiac dilatation and arrhythmias are generally present and the associated pulmonary edema may be refractory to digitalis therapy. This form of heart disease has been found to occur particularly in patients with chronic renal disease who are maintained on low-protein diets. Although the cause of heart disease of this type is not known, excessive accumulation of fluid is generally present and its removal is the treatment of choice. In patients with chronic renal disease digitalis preparations should be used with caution in the treatment of congestive heart failure. Since digoxin is excreted primarily by the kidney, it has a prolonged half-life in patients with severe renal impairment.<sup>6</sup> Therefore, in the presence of severe renal impairment the amount of digoxin should be one-half to two-thirds of the normal dose. Rapid changes in potassium concentration during dialysis therapy also predispose patients with chronic renal disease to digitalis toxicity. For these reasons the congestive failure and pulmonary edema associated with severe chronic renal disease is generally best treated by the combination of sodium restriction, diuretics and, when necessary, fluid removal by dialysis rather than the administration of digitalis preparations.

Pericardial tamponade is another important, reversible factor which may occur in patients with chronic renal disease.<sup>7</sup> It should be particularly suspect in patients with chronic renal failure who seem to have predominantly right-sided cardiac failure with increased jugular venous pressure and hepatic congestion. Inspiratory distension of the jugular vein, referred to as Kussmaul's sign, and *pulsus paradoxus* may sometimes be absent. Patients on dialysis who are undergoing heparinization may be particularly prone to hemorrhagic pericardial tamponade. Pericardiocentesis may be life-saving in these circumstances. If pericardiocentesis is not effective in increasing the systemic arterial pressure and decreasing the venous pressure, then the patient should be taken to surgery for open pericardial drainage.

Patients with chronic renal disease frequently have hypertension, and an episode of accelerated hypertension may cause a rapid deterioration in renal function. Moreover, patients with malignant hypertension and encephalopathy may enter the hospital with signs of cerebral depression and neuromuscular irritability which mimic uremia. Control of the hypertension alone, with or without improvement of renal function, may greatly

improve the clinical status. Controlling the hypertension may also improve renal perfusion and renal function, although in some instances antihypertensive treatment may be associated with a further deterioration of renal function. The most gratifying improvements in renal function are observed in cases in which accelerated hypertension has precipitated congestive heart failure.

Certain electrolyte disturbances, particularly hypokalemia, may worsen the renal function of patients with chronic renal disease. On the other hand hyponatremia may occur in patients with severe renal impairment and be associated with clinical symptoms which mimic uremia but are actually unrelated to a worsening of renal impairment. It should also be noted that acute renal failure may occur on the background of chronic renal failure. In fact acute renal failure may be more likely to develop in diseased than in normal kidneys.<sup>8</sup> The clinical history may be helpful in suggesting an episode of acute renal failure in patients with underlying chronic renal disease. For example, a history of exposure to nephrotoxic drugs, including antibiotics, or a hypotensive episode might suggest the occurrence of acute renal failure. However, the diagnosis of acute renal failure on the background of chronic renal disease can only be confirmed retrospectively on the basis of the clinical course of recovery.

### Abnormalities of Sodium, Water, and Potassium Balance in Chronic Renal Disease

Abnormalities in sodium and water balance are particularly likely to develop in patients with chronic renal disease.<sup>9,10</sup> While most patients with chronic renal disease are able to maintain sodium balance on a normal sodium diet, the institution of a low sodium intake or extrarenal losses of sodium may be associated with volume depletion. On the other hand, these same patients with chronic renal disease may become edematous if placed on a high sodium diet. Thus, patients with advanced chronic renal disease may be poised between edema and volume depletion, and unable to tolerate rapid alterations in sodium balance in either direction. Some patients with chronic renal disease have so-called "salt-losing nephritis" which is featured by an obligatory urinary excretion rate of sodium which exceeds the sodium content of a normal diet. These patients must

therefore ingest large amounts of sodium to maintain sodium balance and avoid volume depletion.<sup>11-13</sup> Cases of "salt-losing nephritis" have most frequently been reported with medullary cystic disease, polycystic disease and pyelonephritis, and they generally occur when the GFR is reduced to less than 10 ml per minute.

Patients with chronic renal disease also have an impaired renal concentration and dilution capacity. Importance of the inability to concentrate urine can be illustrated by the following example. A normal person with a maximal concentrating ability of 1200 milliosmols per liter may excrete a daily solute load of 600 milliosmols in 500 ml of urine per day. In contrast, in advanced chronic renal disease, if the maximum urinary concentrating ability is only 300 milliosmols per liter, then a daily solute load of 600 milliosmols obligates 2 liters of urine per day. Thus, if during a period of extrarenal fluid losses the daily urine output is less than 2 liters, accumulation of solutes, such as urea and creatinine, will occur.

The ability to dilute the urine and excrete a water load is also impaired in patients with chronic renal disease.<sup>14-15</sup> While a normal person may excrete 20 to 30 liters of solute-free water per day without hyponatremia developing, in a patient with advanced chronic renal disease hyponatremia may develop on an oral intake of less than 2 liters per day.

Even with complete suppression of antidiuretic hormone (ADH) and impermeability of the collecting duct the renal capacity to excrete free water is dependent on the volume of fluid delivered to the diluting segment in the distal nephron. In general, this volume approximates 20 percent of the fluid that is filtered at the glomerulus. In a normal person with a GFR of 120 ml per min or 180 liters per day, 36 liters per day would be the approximate volume of fluid delivered to the diluting segment. On the other hand, a patient with severe chronic renal disease and a GFR of 5 ml per min will filter only 7 liters of fluid per day. If 20 percent or 1.4 liters of this filtrate is delivered to the distal diluting segment of the nephron, then this would be the maximal volume of solute-free water which could be excreted per day. Hence, if such a patient is drinking 2 liters or more of water per day, progressive water intoxication and hyponatremia will occur.

"Water-losing nephritis" is a condition which has been described in patients with hypercalcemia or urinary tract obstruction whose urine remains hypotonic to plasma despite the exogenous administration of large doses of vasopressin.<sup>16-18</sup> Such "water-losing nephritis" or "vasopressin-resistant hyposthenuria" also occurs in the majority of patients with severe chronic renal failure.<sup>19</sup> Because of the very low GFR in such patients with advanced renal disease, water-losing nephritis is, however, a somewhat inappropriate term. As illustrated earlier, if a patient is filtering only 7 liters of fluid per day, a maximal "water-losing nephritis" may involve the excretion of less than 2 liters of urine per day. The mechanism for the occurrence of vasopressin-resistance hyposthenuria in any of these circumstances is not entirely clear. An increase in solute load per nephron, structural abnormalities in the tubular epithelium which make these structures unresponsive to the action of ADH (endogenous or exogenous) or the interference of the action of ADH by increased calcium excretion per nephron or some "uremic toxin" have all been entertained as possible mechanisms.<sup>19</sup>

The development of hyperkalemia in chronic renal disease is very rare, unless the patient becomes severely oliguric, receives an acute potassium load or is treated with diuretics, such as spironolactone or triamterine.<sup>20</sup> The ability of patients with chronic renal disease to maintain potassium balance is probably the result of two factors: (1) enhanced potassium secretory capacity of the distal tubule and (2) increased fecal losses of potassium. Evidence for the secretion of potassium is frequently present in patients with chronic renal disease since the amount of potassium excreted in the urine may exceed the amount of potassium filtered at the glomerulus. Hyperaldosteronism in chronic renal disease has been suggested to be the mechanism whereby patients with chronic renal disease are able to increase their distal potassium secretion per nephron and maintain a potassium balance.<sup>20-21</sup> The evidence for a state of "hyperaldosteronism" in chronic renal failure has been based on measurements of aldosterone secretory rates.<sup>22,23</sup> Since this method assumes the excretion within 24 hours of the radioisotopic-labeled conjugate of aldosterone, the delayed excretion of the injected isotope which occurs with impaired renal function<sup>22</sup> makes the results difficult to interpret.



Furthermore, the 24-hour urinary excretion rate of aldosterone in chronic renal disease has been recently found to be within the normal range in patients maintained on a normal sodium diet, and to increase only during prolonged sodium restriction.<sup>24</sup> However, plasma aldosterone levels have not been measured in chronic renal disease. Another factor which allows patients with chronic renal disease to maintain potassium balance is the excessive fecal loss of potassium.<sup>24-26</sup> Patients with severe chronic renal disease may lose as much as 50 percent of their oral intake of potassium in their stool, in contrast to negligible losses (less than 10 percent) in normal persons.

Hypokalemia may occur in chronic renal disease and is most frequently related to the administration of diuretics which increase potassium excretion, such as thiazides, furosemide and ethacrynic acid. Potassium-losing nephritis, like sodium-losing nephritis, is a rare occurrence in chronic renal disease.<sup>27</sup> If the decreased reabsorption of sodium in cases of sodium-losing nephritis occurs in the proximal tubule, then the increased delivery of sodium to the site of potassium secretion in the distal nephron may facilitate the secretion of potassium. Renal tubular acidosis, either the classical type or the variety related to a proximal tubular defect in bicarbonate reabsorption in Fanconi's disease is another cause of potassium wasting in chronic renal disease. Secondary hyperaldosteronism (malignant hypertension, volume depletion, etc.) may also be associated with renal potassium wastage and hypokalemia in chronic renal disease.

### Abnormalities of Acid-Base, Magnesium, Calcium and Phosphorus Metabolism In Chronic Renal Disease

In general the ability to excrete ammonium is limited in patients with chronic renal disease and net acid excretion is less than the estimated endogenous production.<sup>28</sup> Thus, metabolic acidosis is a frequent occurrence in advanced chronic renal failure. Some investigators have suggested that the severity of the metabolic acidosis is in part moderated by the buffering ability of the alkaline bone salts, and that this permits patients with chronic renal disease to compensate for the inability to excrete their daily complement of nonvolatile acid. This buffering activity of bone

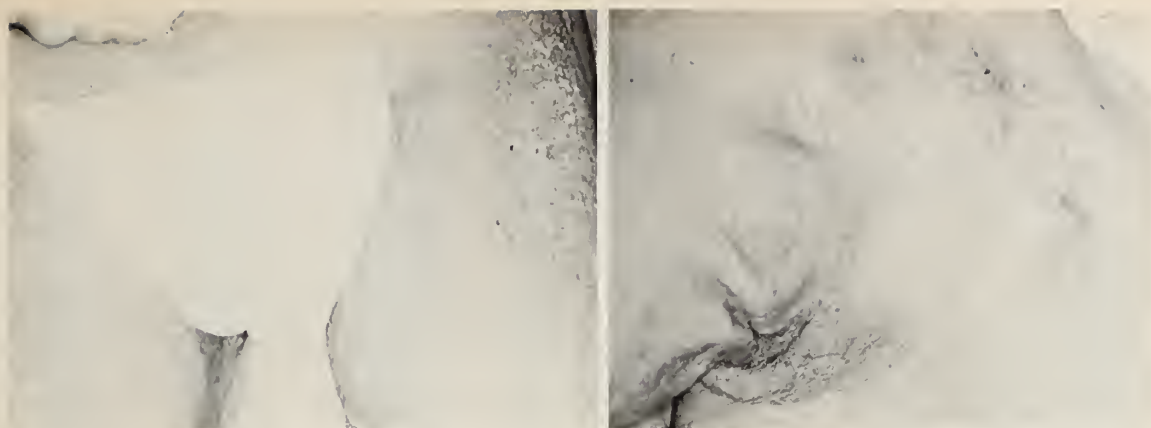
**Table 2.—Disturbances of Calcium and Phosphorus Metabolism in Chronic Renal Disease**

Hypocalcemia
Tetany
Hypercalcemia
Metastatic Calcification
Renal Osteodystrophy
1. Osteomalacia
2. Osteitis Fibrosa Cystica
3. Osteosclerosis

may also be a factor involved in the pathogenesis of renal osteodystrophy in patients with chronic renal disease, which will be discussed later. In general, severe metabolic acidosis necessitating treatment does not occur in steady-state conditions in chronic renal disease. However, as with sodium and water metabolism, the ability to respond to additional stressful circumstances is greatly limited. For example, loss of alkali with diarrhea or increased catabolism, as may occur with fever and infection, may be associated with a rapid appearance of severe acidosis. In these circumstances the metabolic acidosis associated with chronic renal failure must be treated with sodium bicarbonate. The danger of such treatment is obviously related to the increased intake of sodium and the potential precipitation of volume overload and pulmonary edema. The treatment of the acidosis must therefore be carefully monitored with respect to its effect on the cardiovascular system.

Another electrolyte disturbance which may occur in patients with chronic renal disease is hypermagnesemia.<sup>29</sup> Many of the antacids contain magnesium and therefore should not be prescribed in patients with severe impairment of renal function. The symptoms of acute magnesium intoxication include depression of neuromuscular reflexes, hypotension, depression of respirations and ultimately cardiac arrest.

Disturbances in calcium and phosphorus metabolism are frequent concomitants of chronic renal disease (Table 2). Hypocalcemia is generally present in association with hyperphosphatemia. Correction of the elevation of the serum phosphate in chronic renal disease will not, however, uniformly increase the serum calcium concentration to normal levels. The reason for this persistent hypocalcemia is not clear, and it is of particular interest since it occurs in the face of elevated serum levels of parathormone.<sup>30</sup> Whether this hypocalcemia is in any way related



**Figure 1.**—Metastatic calcification in the thigh (left) and axillary (right) region of patient with advanced chronic renal failure.

to excessive levels of thyrocalcitonin in chronic disease remains to be determined. The hypocalcemia of chronic renal disease is rarely associated with tetany and in general need not be treated. This absence of tetany despite significant hypocalcemia is probably due to the fact that the filtrable or ionized portion of the serum calcium is generally normal in patients with chronic renal disease. Tetany, however, may occur in patients with chronic renal disease if the metabolic acidosis is vigorously treated by the administration of sodium bicarbonate. This rapid change in pH may decrease the portion of calcium which is ionized, and precipitate tetany. We have also recently seen a patient in whom symptoms of tetany secondary to pronounced hyperphosphatemia developed following the administration of phosphate-containing enemas in the absence of a decrease in serum calcium concentration.

Hypercalcemia may occasionally occur in patients with chronic renal disease. In general this hypercalcemia is associated with systemic diseases including multiple myeloma, sarcoidosis, metastatic bone lesions, milk-alkali syndrome or vitamin D intoxication. An unusual cause of hypercalcemia recently has been described in the English literature.<sup>31</sup> To avoid the potential danger of a positive sodium balance, calcium (rather than sodium) exchange resins have been used to treat hyperkalemia, and their use has occasionally caused severe hypercalcemia.<sup>31</sup> Autonomous or tertiary hyperparathyroidism may also occasionally be associated with hypercalcemia in chronic renal disease; however, more frequently primary hyperparathyroidism and hypercalcemia have caused the chronic renal disease. After the

occurrence of advanced chronic renal disease it may be difficult clinically to distinguish between these two sequences of events.

Metastatic calcification is another very severe complication of calcium-phosphorus metabolism in chronic renal disease. Metastatic calcification may occur in the kidney, in subcutaneous tissues, in blood vessels and even in the myocardium. This metastatic calcification may be associated with pronounced necrosis of the skin and muscle<sup>32</sup> as well as with gangrene of the distal extremities in some instances.<sup>33</sup> Severe metastatic calcifications in the thigh and axillary regions of a patient with advanced chronic renal failure is illustrated in Figure 1. The incidence of the metastatic calcification seems to be in general related to the degree of elevation of the calcium-phosphorus product. The calcium-phosphorus product in patients with chronic renal disease therefore should not be allowed to exceed 60 milligrams per 100 ml. The best means of lowering this product is to lower the serum phosphate level by the administration of nonmagnesium containing phosphate binding antacids which will increase the fecal losses of phosphate.

Renal osteodystrophy is a very frequent complication of advanced chronic renal disease when diagnosed on histological grounds by bone biopsy.<sup>31-35</sup> On the other hand, radiological evidence of renal osteodystrophy is less frequent and symptomatic renal osteodystrophy even more infrequent. However, a small proportion of patients with advanced chronic renal failure will have severe bone pain and evidence of pathological fractures. In general there are three varieties of bone disease which may occur in





Figure 2.—Renal osteodystrophy: “salt and pepper” pattern in the skull (left) and subperiosteal resorption in distal phalanges in patient with advanced renal failure and secondary hyperparathyroidism (right).

chronic renal disease, namely, osteomalacia, osteitis fibrosa cystica (which is indistinguishable from the bone disease that occurs with primary hyperparathyroidism) and osteosclerosis. All three types of bone disease may, and generally do, occur in the same patient. The presence of severe osteitis fibrosa cystica in a patient with chronic renal failure is illustrated in Figure 2. Both the “salt and pepper” appearance in the skull and the subperiosteal reabsorption in the distal phalanges are characteristic of this form of renal osteodystrophy. It has been postulated that renal osteodystrophy is caused by resistance to vitamin D. Although normal blood levels of vitamin D have been found in patients with chronic renal disease,<sup>36</sup> a defect in calcium absorption from the gastrointestinal tract has been shown to occur in most of these patients.<sup>37</sup> In normal persons approximately 80 percent of the calcium in the diet appears in the stool; however, in patients with chronic renal disease nearly 100 percent of the oral intake of calcium may be recovered from the stool. Although patients with chronic renal disease excrete very little calcium in the urine,<sup>19,38</sup> the total urine and fecal calcium losses may exceed the oral intake of calcium. This small, daily negative calcium balance over a long period may be an important factor in the pathogenesis of renal osteodystrophy.

Administration of large doses of vitamin D has been shown to increase the gastrointestinal absorption of calcium in chronic renal disease, and this positive calcium balance is associated with improvement in the bone disease. The danger

of the administration of vitamin D in chronic renal disease is that prolonged hypercalcemia and metastatic calcification may occur. This complication may be difficult to treat because the half-life of vitamin D may be several weeks in patients with chronic renal failure. The occurrence of hypercalcemia with vitamin D therapy is most frequently seen in patients with chronic renal disease who have a normal serum calcium concentration before vitamin D therapy, and thus perhaps the most pronounced secondary hyperparathyroidism.<sup>39</sup> In some of these patients parathyroidectomy may be necessary before treatment with vitamin D is begun.

While it is quite clear that large doses of vitamin D may improve the bone disease in patients with chronic renal disease, this does not necessarily implicate “vitamin D resistance” as the main pathogenetic factor in the osteodystrophy. In fact a recent study suggests that the defect in calcium transport in the intestine during uremia is independent of either intestinal calcium binding protein or vitamin D activity.<sup>40</sup> Moreover, de Wardener and associates<sup>41</sup> have been able to improve the bone disease in chronic renal disease by the oral administration of calcium carbonate or calcium phosphate salts. In these studies a positive calcium balance occurred in the absence of vitamin D administration. Since the administration of vitamin D, calcium salts or parathyroidectomy may be associated with complications, only patients with symptoms of renal osteodystrophy or severe radiological evidence of renal osteodystrophy should be treated. In

children the decision concerning treatment is more acute because the renal osteodystrophy may be associated with stunting of growth and abnormalities of gait.

Neuromuscular Disturbances in Chronic Renal Disease

The neuromuscular disturbances which occur in patients with advanced chronic renal failure are the hallmark of clinical uremia. Occurrence of neuromuscular symptoms provides the best evidence that the medical management has been inadequate, and either reversible factors must be found and treated or more definitive therapy, such as chronic dialysis or renal transplantation, be instituted. Some of the neuromuscular disturbances associated with uremia are somewhat subtle, such as increased emotional lability, insomnia or inability to concentrate, while other symptoms, such as asterixis, coma and convulsions are more dramatic. If the more subtle symptoms can be detected, treatment can be started in time to avert the life-endangering symptoms of coma and convulsions. Although a specific "uremic toxin" which causes the central nervous system manifestations of uremia has not been identified, in experiments with dogs these symptoms have been simulated by the chronic administration of guanidinosuccinic acid.<sup>42</sup>

Both sensory and motor peripheral neuropathy may develop in patients with chronic renal disease.<sup>43</sup> One of the first findings is the "restless leg syndrome"<sup>44</sup> or paresthesias in the distal extremities.<sup>43</sup> The motor involvement generally occurs later and may progress to either para- or quadriplegia. In most instances dialysis will either arrest or even improve the sensory peripheral neuropathy but motor neuropathy may be irreversible.<sup>45</sup> The pathogenesis of the neuropathy seems to be unrelated to either diabetes mellitus or vitamin deficiency and the responsible mechanisms remain to be explained. Histologically, the damage in the peripheral nerve occurs in the distal portion of the myelinated fibers and involves a loss of myelin. This histological finding has raised the possibility that there is a decrease in delivery of some necessary component of metabolism to the distal part of the nerve fiber but this hypothesis remains to be proved.

Significant delay in the nerve conduction time may be used as a criteria for the institution of more definitive management, that is, renal trans-

Table 3.—Hematological Disturbances in Chronic Renal Disease

I. Anemia
A. Hemolytic Component
1. Extracorporeal Factor
B. Decreased Erythropoiesis
1. Low Erythropoietin Levels
2. Suppressive Effect of Transfusions
C. Iron Deficiency
D. Folic Acid Deficiency
II. Hemorrhagic Tendency
A. Gastrointestinal Irritation with Ammonia
B. Platelet Defect
1. Inhibition or Destruction of Platelet Factor 3

Table 4.—Carbohydrate and Lipid Disturbances in Chronic Renal Disease

I. Carbohydrate Intolerance in Uremia
A. Normal Fasting Blood Sugar
B. Abnormal Glucose Tolerance Test
1. Insulin-resistance Secondary to Peripheral Antagonism
II. Hypertriglyceridemia
A. Increased Hepatic Synthesis of Triglyceride-rich Lipoprotein
B. Decreased Post-heparin Lipolytic Activity

plantation or chronic dialysis.<sup>45,46</sup> Some other neuromuscular disturbances which occur in chronic renal failure are acute blindness, nystagmus, miosis and pupil asymmetry.<sup>43</sup>

Hematological Disorders in Chronic Renal Disease

Hematological disorders (Table 3) are a very frequent occurrence in chronic renal disease, and anemia in particular occurs in almost every case. In fact, if a patient enters the hospital with severe renal impairment and a normal hematocrit, an acute cause of the renal failure should be considered. In general, transfusions should not be used to treat the anemia, since the administration of multiple transfusions is associated with numerous complications including transfusion reactions, hemosiderosis, viral hepatitis and suppression of erythropoiesis. In the absence of multiple transfusions, the hematocrit in patients with advanced renal failure will generally stabilize in the range of 20 to 25 values percent, a level which is well tolerated unless the patient has severe arteriosclerotic cardiovascular disease.

The anemia seems to be etiologically related to two factors, namely, hemolysis and suppression of erythropoiesis.<sup>47,48</sup> Chart 2 shows the correlation between the shortened half-life of chromium-tagged red blood cells and the degree



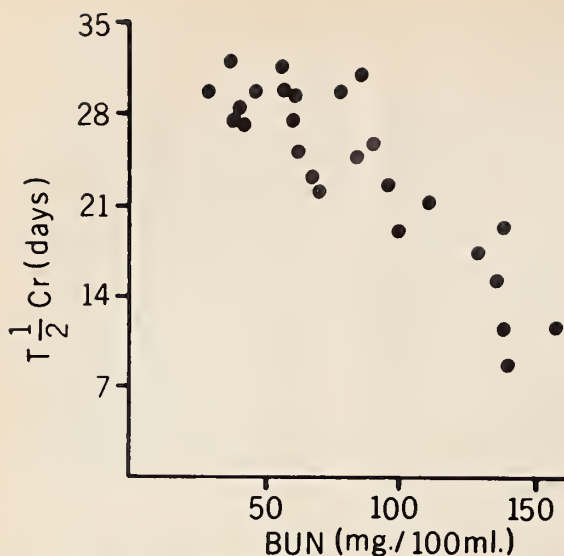


Chart 2.—Relationship between shortened half-life of chromium-labeled red blood cells and BUN in chronic renal failure. Reproduced with permission of publisher.<sup>49</sup>

of the azotemia.<sup>49</sup> The cause of this hemolysis seems to be related to an extracorporeal factor. Red blood cells from uremic patients have a normal half-life when transfused into normal subjects. Conversely, red blood cells from normal subjects have a shortened half-life when transfused into uremic patients. The degree of hemolysis is, however, relatively mild and with a normally functioning bone marrow would not lead to any significant degree of anemia. Thus the suppression of erythropoiesis seems to be the most significant factor in the anemia of chronic renal disease. Bioassays of erythropoietin have indicated that patients with chronic renal disease have considerably lower blood levels of erythropoietin than normal subjects. Thus, decreased erythropoietin levels have been suggested as a cause of the suppression of erythropoiesis in chronic renal failure. However, measurable increases in erythropoietin levels have not been uniformly found in dialysis patients who have demonstrated an increase in erythropoiesis and hematocrit after control of uremia with dialysis and withholding transfusions for six months to two years.<sup>50</sup> Therefore, while the suppression of erythropoiesis may be related in part to a decrease in erythropoietin production, additional factors may be involved.

An additional cause of anemia in chronic renal disease is iron deficiency which may be due to blood loss from the gastrointestinal tract or into

the dialysis machine. Folic acid deficiency has also been described as a cause of anemia in patients with chronic renal disease on maintenance dialysis.<sup>51</sup> Another hematological disorder which is well known to occur in patients with advanced renal failure is an increased hemorrhagic tendency. Gastrointestinal hemorrhage may be related to the direct chemical irritation of urea on the mucosa; however, the overall hematological tendency of renal failure has been related to an inhibition of destruction of platelet factor 3.<sup>52</sup>

### Disorders of Glucose and Lipid Metabolism in Chronic Renal Disease

Approximately 70 percent of patients with uremia have an abnormal glucose tolerance test. This "uremic diabetes" does not seem to be related to an inability of the pancreas to secrete insulin, since the initial response of plasma insulin levels to intravenous glucose is decreased in diabetic patients and is normal in patients with uremia. This finding has led most investigators to feel that "uremic diabetes" is due to an antagonism of the peripheral action of insulin. *In vitro* dialysis of uremic serum has failed to abolish this insulin-resistance, as assayed on rat diaphragm.<sup>53</sup> However, chronic dialysis in patients is known to normalize the glucose tolerance test in uremic patients.<sup>54</sup> These findings suggest that the antagonism to the action of insulin in uremic patients is at the level of the peripheral tissues rather than antagonism by a circulating substance. The clinical importance of the glucose intolerance in patients with uremia is related to the problems of selecting patients for chronic dialysis and renal transplantation. Patients with diabetes mellitus are in general less suitable candidates for this more definitive treatment because of their high incidence of progressive vascular complications. The measurement of the fasting blood sugar is an easier means than measuring plasma insulin levels to differentiate true diabetes mellitus from "uremic diabetes." While the fasting blood sugar is abnormal in patients with diabetes mellitus, it is generally normal in patients who demonstrate the glucose intolerance of uremia. (See Table 4.)

Hypertriglyceridemia is another metabolic abnormality which occurs in association with chronic renal disease.<sup>55</sup> The cause of this hypertriglyceridemia seems to be related to both an increase in hepatic synthesis of triglyceride-rich

lipoprotein and the decreased clearing activity of lipoprotein lipase. The clinical significance of this hypertriglyceridemia remains to be established.

In summary, the medical management of patients with chronic renal disease is a very important aspect of their care. The clinician must search for and treat reversible factors which may improve or prevent further deterioration of renal function. If such reversible factors are not found and treated, advanced renal failure may be associated with abnormalities in virtually every organ system and make the medical management very difficult even for the most astute of clinicians. As Homer Smith<sup>56</sup> put it in his book *From Fish to Philosopher*:

Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival; but should the kidneys fail . . . neither bone, muscle, gland, nor brain could carry on.

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### Automated and Programmed Services in Health Care

AN ARTICLE PUBLISHED in this issue serves to draw attention to the uses of automated and programmed services in health care. The Bureau of Research and Planning Report "Multiphasic Health Testing—1971" provides an excellent overview of the subject particularly as it pertains to California. Multiphasic screening or multiphasic health testing is only one of the many uses of automated and programmed services in health care, although it seems at the moment to have acquired most of the charisma. Automated instrumentation and "programmed" personnel have been widely used to perform many other services in health care, for example, in clinical laboratories which are increasingly being automated, and in coronary care units where both instrumentation and personnel are programmed to perform in predetermined fashion in specified situations. Such kinds of automated and programmed services have been found not only acceptable but necessary.

It is safe to say that we have probably only begun to scratch the surface of the possible uses of this technology and these techniques in health care. This became quite evident during the discussions at the National Invitational Conference on AMHTS (Automated Multiphasic Health Testing and Services) sponsored by the National Center for Health Services Research and Development (DHEW) early last year. It was recognized there that it is fully as important to use automated and programmed services to increase the capacity of an overburdened delivery sys-

tem as it is to use them for screening to detect disease, which when found and followed up, often adds substantially to the load of an already overworked health delivery system. The experience of large and growing demands for more products and more services is nothing new in our technological society and the response of the providers, business and industry, has been to automate what can be efficiently automated and to program what can be effectively programmed, and where possible to eliminate the wasteful use of costly resources, particularly personnel. The parallel of this with many of the problems in health care delivery seems obvious.

None of this is to say that automated and programmed services in health care ever can or ever should displace the essential functions of the physician, the nurse, or the pharmacist for that matter, but rather that under appropriate conditions certain routine and repetitive functions can be performed by programmed instrumentation and personnel who are specially trained for the specific purpose. This can relieve more highly trained and relatively scarcer personnel of these tasks and enable them to do more of those things in health care which are essential and which only they can do. In fact it is quite likely that only in this way will it ever be possible to overcome the relative "shortages" of physicians, nurses and other highly trained key personnel in the face of spiraling demands for services.

There are many apprehensions concerning the use of automated and programmed services in health care. There are fears that medicine will become depersonalized, that the computer or other professionals will "take over," that the costs will be excessive, or that such things as the doctor-patient relationship and confidentiality will simply disappear. Yet the fact remains that there are many tasks which could be performed far more efficiently and effectively. The volume of paper work in physicians' offices, clinics and hospitals is already almost choking the delivery sys-

tem, and this is likely to get worse rather than better. There are also cultural, language, educational and distance barriers to consumer access to services which are substantial and have somehow to be overcome in both rural and urban communities. There must be many ways in which automation and programmed services can be used to help solve some of these problems, while maintaining and even improving personalization and individualization where this is necessary.

It is suggested that automation and programmed services should *only* be used in health care when they may be expected to (1) increase the reach or productivity of physicians, of other scarce personnel or of a community health care delivery system so that a larger number of persons will receive a better level of care than would otherwise be the case; (2) achieve economies in the cost of each service rendered because of the volume of usage, often referred to as economy of scale; and (3) promote quality through professional control of the subject matter or content of the automated or programmed service to be rendered. If these guideposts of improved access, cost containment and quality assurance can be followed, then these services will become useful and acceptable adjuncts to community health and patient care, and there will need be no fear of control of health care by any sort of non-thinking, impersonal, automated monster or system.

M.S.M.W.

## The Marijuana Problem

THE EPIDEMIC-LIKE SPREAD of the use of marijuana in the United States in the past few years has caused a great deal of anxiety in the public. The extensive use of marijuana that was first seen on college campuses has spread downward into the high schools and the elementary schools and into the communities where it now is not

confined to any age, social or occupational group.

In the past, marijuana use was frequently associated with psychopathy and most narcotic addicts gave a history of having used marijuana before starting on "hard" drugs. Passage of the Marijuana Tax Act in 1937, the listing of marijuana along with opium and coca leaves on the Special Tax Stamp, and the removal of marijuana from the United States Pharmacopoeia and the National Formulary in 1941 gave the impression that marijuana was a "narcotic," that it was addicting and therefore dangerous. It became extremely difficult for investigators to obtain either a license or the drug, and research on the drug for all practical purposes ceased.

It was known that practically all hippies used marijuana and that many of the youngsters who were dropping out of school or developing into serious behavior problems at home were using drugs.

Harsh penalties, intensified police activity to apprehend the law-breaking marijuana user, statements about dangers issued by the Committee on Problems of Drug Dependence of the National Research Council and the Committee on Alcoholism and Drug Dependence of the AMA Council on Mental Health, warning by the World Health Organization, and educational programs in schools had little or no effect in stemming the rising tide of marijuana use.

The use of marijuana was associated with experimentation with many other drugs—LSD, peyote, mescaline, amphetamines, barbiturates, hashish and the volatile component of glues. Increasing numbers of parents seeing their children behaving peculiarly suspected they were using drugs, but were at a loss to know what to do.

Physicians who were consulted by concerned parents, law enforcement officers and legislators often expressed opinions about the drug which were based on prejudices rather than knowledge, or on "the little knowledge" that proverbially is a dangerous thing.

Many conflicting opinions were expressed. There were many respected lawyers and teachers who advocated legalizing marijuana. Many investigators urged caution in coming to any conclusion regarding the effects of continued marijuana use, pointing out that no reliable long-term studies had been done. Revolutions in dress, in sexual behavior, in manners, and in attitudes toward life, authority figures and the



establishment developed simultaneously with the increase in use of marijuana. This explains in part the feeling that marijuana use is an expression of rebellion against parents and the establishment, and indicative of a social change that is of even greater concern at present than the impairment of health that may result. Some observers have felt that the illegality of marijuana was a motivating force rather than a deterrent.

It has become obvious that to look upon the people who use marijuana as all alike would be as unfounded as thinking of all those who use alcohol as being the same.

Marijuana is used for a wide variety of reasons. Some people have tried it out of curiosity and quit. Some continue to use it sporadically on the urging of friends or because of a wish to belong. Some use it occasionally for relaxation, some for stimulation and some for socializing and to remove inhibitions. The intoxication that is experienced seems to be associated with a transient toxic encephalopathy that produces measurable changes in some aspects of brain function that are described in Dr. Chun's excellent review article on marijuana in this issue.

The effects that are sought by the social user seems to be euphoria or feeling of well-being, a decrease in social anxiety, sharing an experience and often an increased sensual experience with music, colors, or beauty. Social users hardly ever have a bad reaction or, as far as is now known, any serious long range ill effect—or habituation.

There are those, however, who have used marijuana frequently over a long period primarily as an escape from reality or as a means of making life tolerable. These users, who are dependent on marijuana and almost without exception use other drugs, too, in some respects, resemble chronic alcoholics but are often more disturbed. The other drugs they use produce far more problems than the marijuana.

Studies of personalities of users and non-users on a college campus revealed far less in the way of differences than would be expected. Even chronic users were found to be doing well in their work and in their lives. They did not show the poor motivation, the apathy and relaxed drifting that has been described by some observers as a frequent complication. It is possible that some portion of those who may have been so affected have dropped out of school, but the size of this group is simply not known.

There is no doubt about the existence of very serious emotional disorders in some chronic marijuana users (or abusers). Some have severe personality disorders and some are borderline or overt schizophrenics. Many need to be treated in hospital for severe disabilities. Many were clearly ill before they started using marijuana (and other drugs). In some instances a psychiatric illness appears to be precipitated by excessive drug use (including marijuana) but even here pre-existing significant psychopathology is the rule rather than the exception. It is not unusual to see a patient who has used marijuana to escape from reality. Some patients decompensate while seeking mystical experiences or psychological insights. Acute psychiatric reactions following marijuana use have been described. However, they are rare and clear up rapidly with treatment when the predisposition was not great. Hekimian and Gershon<sup>1</sup> reported that 50 percent of drug abusers who were admitted to Bellevue Hospital had been schizophrenic before taking drugs.

The widespread use of marijuana is still so new that there is as yet no reliable data on the effects of frequent, continued use. Prospective studies may help in distinguishing between the roles of premorbid personality and drug effect in persons who show adverse reactions.

Animal experiments indicate that, as compared with alcohol or barbiturates, marijuana is an unusually safe drug. Huge doses have been given without causing death. Nor have there been any reliable reports of human fatalities. The Indian Hemp Commission that studied the problem of marijuana use over 75 years ago<sup>2</sup> concluded after a most careful and exhaustive investigation that there was no connection between marijuana and violent crime and that *moderate* use produced no moral injury. The Commission concluded that "excessive consumption, on the other hand, both *indicated* and *intensified* moral weakness and tended to lead to loss of self respect, occasionally to dishonest practices that were associated with degraded poverty but rarely with violent crime." There was no evidence of its producing chronic insanity except as might occur with chronic excessive use of alcohol.

It seems clear that marijuana is not addictive. Its use does not result in physical dependence. Tolerance does not develop and discontinuance of marijuana does not produce withdrawal symptoms. Nevertheless, as McGlothlin<sup>3</sup> and others

have pointed out, the concern about marijuana is not limited to the harmful effects that drug abuse may produce in individuals, but to the burdening of society with the care and support of persons who may become disabled. But of even greater importance is the possibility that marijuana abuse is a new form of disaffection—a symptom of dissatisfaction with the present values, ethics and direction of society, the solution of which lies in the resolution of some of the major conflicts between the younger and older generations, such as those about the Vietnam war.

Not only is there a need to maintain an unbiased perspective about the “pot scene” that has been unfolding, but a need to develop imaginative controls to replace the punitive approaches that seem to have aggravated rather than solved the problem.

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## Leukemia in Childhood

A LITTLE OVER 20 years ago the first leukemic child was treated with methotrexate and the age of modern chemotherapy was ushered in. Before the use of the effective anticancer drugs, a child with acute leukemia might expect to survive perhaps three months. At that point in time it was not at all certain that medical therapy conferred any benefit at all. The road since has been arduous and expensive, but has generally led in the right direction. Only in the last few years has the physician been able to say with

confidence that it is more humane to the leukemic child to treat his disease aggressively than to leave it untreated. This is the central theme of the Specialty Conference on childhood leukemia published in this issue of CALIFORNIA MEDICINE.

By the early 1950's the introduction of the folate-antagonists had indicated a new direction and within a few years median survival had increased to six months. The subsequent milestones in treatment were: the introduction of corticosteroids and 6-mercaptopurine between 1950 and 1955; the start of combination chemotherapy and the simultaneous demonstration of the efficacy of platelet transfusions in the early 1960's; the evolution of sophisticated programs of “maintenance” and “consolidation” therapy in the decade between 1960 and 1970; and finally within the last few years, the demonstration of a new mode of chemotherapeutic attack with L-asparaginase—an attack which takes advantage of a biological difference between normal and malignant leukocytes.

The investment in trying to improve therapy has been massive in terms of physicians' efforts and money spent. The emotional price paid by the parents and children cannot be quantitated. The results of this effort are that the median survival in the best centers is now about three and a half years and a small minority of patients are apparently cured of their disease. However, a majority of patients still die of leukemia, usually from the same complications that caused most deaths before the use of chemotherapy—hemorrhage and infection.

With the greater availability and more intelligent use of platelet transfusions, hemorrhage as a cause of fatality has been strikingly reduced. Infection remains, however, as a major cause of death. It is usually the consequence of too few normal granulocytes. The rapid advances achieved by chemotherapy have now plateaued, largely because “obliterative” therapy is limited by the destruction of normal bone marrow elements and, in particular, the granulocyte.

Clearly, this is one of the areas for future clinical research. The means of providing granulocytes are theoretically at hand. Pilot programs have already demonstrated that normal or *mature* leukemic granulocytes can function to combat microbial infection when antibiotics have failed. We should now be implementing



investigative programs for the procurement, storage and distribution of granulocytes. This must be the next phase in the attack on leukemia.

Are there other clear directions for the future? The demonstration with L-asparaginase that there exists an exploitable biochemical difference between the normal and the leukemic cell has opened up a new vein of clinical therapy and research which has hardly been tapped. Even more exciting is the recent demonstration (1) that a component of deoxyribonucleic acid (DNA) synthesis of leukemic cells (but not of normal cells) may be directed by ribonucleic acid (RNA) rather than by the usual DNA primer—a demonstration that perhaps will etiologically implicate an RNA virus in human leukemia. The possibility of using antibiotics which specifically interrupt this RNA-directed sequence of DNA synthesis or of an anti-viral vaccine are now clearly within the realm of possibility.

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## The Politicization of Health Care

THE POLITICIZATION OF HEALTH CARE, which was both predicted and feared, has come to pass. It is now all too evident in both State and Nation. Some argue that this is good, that health care is too important to be left to the professionals, to the health care industry, or even to the individual citizen, and that it is not only desirable but essential that its governance be a function of our political system. Others take an opposite position,

that it has yet to be demonstrated that government with its politics and bureaucracy can run anything economically or efficiently, let alone with the sensitivity and personalization which is so necessary in such a thing as the care of an individual who is sick or injured. But the large scale financial involvement of government and others in personal health care made politicization inevitable, with the result that the sick or injured patient, who by law or circumstance is locked into a politicized system of health care, often becomes a helpless and hapless victim of political conflict.

It is true that health, first in the sense of the absence of disease or infirmity and then in the sense of physical, emotional and social well-being, can be the grand accomplishment of any political system if this can be achieved for all its people. In the present battles over health care, one can see both the grandeur and the ineptness of a political system with lofty goals and far too little understanding of the complex ramifications of the problems to be solved. The tragedy is that the victims are more often than not the very persons or institutions the whole political effort is supposed to serve.

The politicization of health care will not go away. Nor will the hapless victims of its struggles. Nor will the concern of physicians with their patients. It is worth noting that at any one time the majority of voters are not sick, they are well; and therefore it is to the well, not the sick or injured, to whom the politicians will make their appeals. So it is essential that there be a strong advocate for the sick and injured, victims who themselves cannot be effective in the political arena. This is a natural and appropriate responsibility for physicians and the medical profession. The California Medical Association has properly assumed this role. It is to be congratulated. The formidable list of amici curiae who joined the recent CMA court action in behalf of Medi-Cal patients is both tangible and gratifying evidence of wide support for this important CMA action.

# CASE REPORTS

## Partial Tracheal Obstruction Due to Anomalous Origin of The Left Pulmonary Artery

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PACUILLI, M.D., FRANCIS Y. K. LAU, M.D.,  
VICTOR G. MIKITY, M.D., AND  
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VASCULAR RINGS are an important and curable cause of extrinsic tracheal obstruction in the infant. The usual types of vascular rings formed by the aortic arch and its major vessels at the level of the upper trachea are well known. Herewith is a case report of the less-well-known vascular ring formed by the pulmonary arterics at the level of the tracheal bifurcation. Obstruction of the bifurcation of the trachea by a pulmonary vascular ring or sling was first described by Glaevecke and Doehle in 1897.<sup>1</sup> To date 51 cases have been reported in the literature.<sup>2-34</sup>

In this anomaly the right pulmonary artery arises normally from the main pulmonary trunk, passes anterior to the bifurcation of the trachea, and crosses normally over the right main stem bronchus. The left pulmonary artery does not arise from the main pulmonary artery trunk, but arises from the right pulmonary artery, where it

crosses over the right bronchus. The left pulmonary artery passes between the trachea and esophagus to the left lung (Figure 1). This traps the trachea between the right pulmonary artery in front and the left pulmonary artery behind.

### Report of a Case

The patient, an infant, was the product of a full-term, normal gestation. Delivery was normal. The apgar was 8 and the birth weight was 3100 grams. Respiration was spontaneous, and there was no respiratory distress until the patient was five days old. An x-ray film of the chest at that time (Figure 2) showed a hyperlucent left lung. The patient was noted to have tachypnea and respiratory wheezing. At six weeks of age, the infant was admitted to hospital because of

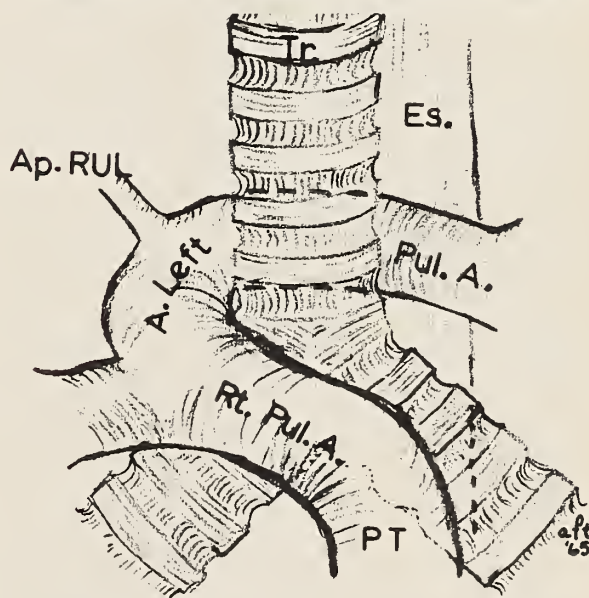


Figure 1. — Sketch from pulmonary angiogram showing left pulmonary artery crossing in front of right main stem bronchus, and then passing posterior to the trachea and anterior to the esophagus to the left lung. Abbreviations: A. Left Pul. A.=Left pulmonary artery; Ap. RUL=Right upper lobe branch; Es.=Esophagus; PT=Pulmonary trunk; Rt. Pul. A.=Right pulmonary artery; Tr.=Trachea.

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**Figure 2.**—X-ray film of chest at age five days. There is pulmonary overexpansion on the left. Heart normal.

respiratory distress at rest. Cyanosis was absent, but there was tachypnea, subcostal retractions, wheezing and stridor. The pH,  $p\text{CO}_2$ ,  $p\text{O}_2$ , and serum bicarbonate levels were normal. A roentgenogram of the chest at that time was interpreted as moderate pulmonary overexpansion on the left (Figure 3). No abnormality was noted on laryngoscopic examinations. Bronchoscopy showed a narrowing of the trachea approximately 1 cm below the glottis in the region of the posterior wall, and a 3.5 mm bronchoscope could not be passed through the narrowed area. Bronchography, combined with an esophagram, revealed a posterior imprint on the trachea, with narrowing and an anterior imprint on the esophagus at the level of the carina (Figure 4). The bronchogram demonstrated the distal trachea to be of small caliber, and the diagnosis of hypoplasia was suggested.

From the age of six weeks, the infant was continually being put into hospital because of respiratory distress. There were numerous episodes of apnea and cyanosis, not associated with choking, but occurring during feeding. The attacks were terminated by oral pharyngeal suction. At age four months, the apneic episodes had become more frequent and were now accompanied by cardiac arrest. Cardiac catheterization and pulmonary angiography (Figure 5) demonstrated an anomalous left pulmonary artery, with no associated congenital heart disease. Surgical correction of the vascular sling was carried out. The immediate postoperative course was complicated by numerous respiratory and cardiac



**Figure 3.**—X-ray film of chest at age six weeks. There is pulmonary overexpansion, particularly left upper lobe. Heart normal.

arrests. The patient died four hours postoperatively with airway obstruction. Permission for autopsy could not be obtained.

## Discussion

A review of 52 cases shows that in 47 of them an anomalous left pulmonary artery produced symptoms of major airway obstruction. The onset of symptoms was from birth to two years, with onset under one month of age in 23 cases. The symptoms were usually tachypnea or dyspnea and stridor, as well as apneic episodes. Choking, with regurgitation, was sometimes associated with feeding. In 41 of 43 patients, the symptoms were progressive. The progression seemed a more significant indication of a poor prognosis than either the age of onset or the duration of symptoms.

In approximately half of the cases, the physical examination suggested unilateral airway disease, usually on the right, occasionally on the left, and sometimes bilateral. Chest radiographs reveal no characteristic findings and are reported as: normal; unilateral overexpansion, either right or left, and sometimes bilateral; atelectasis; mediastinal mass-like lesions; unusual hilar shadows, and the like. The esophagram reveals an extrinsic pressure defect on the anterior wall of the barium-filled esophagus at the level of the carina (Figure 4). Patients with non-constricting anomalies of the left pulmonary artery apparently do not have respiratory complaints, and



Figure 4.—Combined bronchogram and esophagram. *Left*, frontal view shows narrowed distal trachea for distance of approximately 2.5 cm above level of carina. Left and right main stem bronchi are of larger caliber. *Right*, lateral view reveals narrowed distal trachea and separation of lower trachea and esophagus by the aberrant left pulmonary artery (arrow).

esophagographic studies are normal.<sup>27</sup> Anterior wall imprints on the esophagus may be caused by bronchial cysts, reduplication cysts of the esophagus, and by unusual lymph node enlargement. Although these are extremely rare, pulmonary angiography establishes the diagnosis of an aberrant pulmonary artery.

The embryologic origin of this anomaly appears to be related to a sequential change during the formation of the left pulmonary artery and the primitive left lung bud. If growth of the left pulmonary artery is delayed, or if the primitive left lung growth is accelerated, they cannot align normally. In order to establish its mesenchymal connection, the primitive left pulmonary artery would have to pass anterior to the right bronchus, posterior to the trachea, then to the left lung bud because its normal pathway would be obstructed by the overgrown left primitive bronchus.<sup>2,9</sup>

Potts et al<sup>5</sup> were the first to perform a successful surgical correction of the anomaly. They divided the aberrant left pulmonary and re-

anastomosed it in front of the trachea. Hiller and Maclean<sup>8</sup> ligated the aberrant left pulmonary artery at its origin and anastomosed its distal end to the broadside of the main pulmonary artery. Mustard<sup>17</sup> divided the ligamentum arteriosum and obtained relief of symptoms. Lochard et al,<sup>19</sup> however, found that in their case, because of the lower position of the aberrant left pulmonary artery in relation to the right main bronchus and trachea, it was only necessary to section the former and to bring forward the anomalous vessel. The right bronchus was then re-anastomosed. The majority of operations have been of the Potts variety.

Fifteen of 21 patients survived surgical intervention and eventually improved, whereas no patients with major airway obstruction have survived with only supportive therapy. A number of patients, including ours, did not have relief of the airway obstruction even though the anomalous pulmonary vessel was surgically corrected. In two patients,<sup>23,32</sup> who died immediately postoperatively, complete cartilaginous rings were





Figure 5.—Pulmonary angiogram. *Left*, frontal angiogram shows the origin of the left pulmonary artery from the right pulmonary artery (arrow). Right upper lobe pulmonary artery (arrow with bars) arises from proximal portion of aberrant left pulmonary artery. *Right*, lateral angiogram shows retrotracheal course of the aberrant left pulmonary artery (arrow).

present. Four other patients<sup>2,15,16</sup> with complete cartilaginous rings died without surgical intervention. One might postulate that patients with complete cartilaginous rings would have an extremely poor prognosis regardless of treatment. As was previously noted, autopsy was not done in the case herein reported. However, the bronchogram revealed a very small-caliber trachea—hypoplastic trachea—(Figure 4), and a 3.5 mm bronchoscope could not be passed. One might speculate as to whether constant pressure by the anomalous left pulmonary artery on the airway might interfere with its development, and, thus, be responsible for complete cartilaginous rings or hypoplastic development of trachea or bronchi.

## Summary

A case of tracheal obstruction due to a vascular sling produced by an anomalous origin of the left pulmonary artery from the right pulmonary artery is presented. The diagnosis was suspected from the plain films and esophagram, and was confirmed by angiography. When tracheal hypoplasia or complete cartilaginous rings are present, the prognosis is very grave, despite any mode of surgical repair of the anomalous origin of the left pulmonary artery.

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## Mediastinal Emphysema During Diabetic Ketoacidosis

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DIRECT COMPLICATIONS of diabetic ketoacidosis, such as hypovolemic renal failure and extremes of serum potassium, are well known to practicing physicians. In addition to the anticipated metabolic derangements, concomitant problems such as gastric or intestinal atony, seizures, cerebral edema, acute flaccid quadriplegia or severe muscular weakness, polyneuropathy or fulminant infections are occasionally encountered. The following brief case report illustrates yet another apparently associated complication of diabetic ketoacidosis, mediastinal emphysema.

### Case Report

A 12-year-old Caucasian boy was admitted to a small private hospital on 20 October 1968 with

a history of loss of 15 pounds in weight over a period of three weeks and a two-day period of intense thirst, irritability, abdominal pain of a diffuse nature and vomiting. Until then the patient had been in excellent health. He was not known to be diabetic and family history was negative in this regard. He was an only child.

On physical examination he appeared anxious and was hyperventilating. Temperature was 35.6° C (96° F), pulse of 160 per minute, blood pressure of 120/60 mm of mercury and respirations 40 per minute and deep. The eyeballs were sunken in the orbits and mucous membranes were dry. The neck was supple without adenopathy and there was no subcutaneous emphysema. With the patient supine the neck veins were not distended. The chest was clear. Cardiac tones were heard well and the left heart border was within the mid-clavicular line. A loud crunching type of sound was heard along the left sternal border synchronous with systole. The abdomen was flat, bowel sounds were absent, and there was moderate guarding with no rebound tenderness. All peripheral pulses were intact. The skin was warm and dry. The neurological examination was unremarkable except for pronounced agitation and at times confusion. The patient's breath had a strong acetone odor.

Results of laboratory studies at the time of admission were: hemoglobin 15.2 grams per 100 ml; hematocrit, 45 percent; white blood cell count 20,000 per cu mm with a shift to the left; blood urea nitrogen 21.8 mg per 100 ml; blood glucose 575 mg per 100 ml; blood acetone positive at a 1:8 dilution; serum sodium 135 mEq per liter; serum potassium 5.2 mEq and serum bicarbonate 6.3 mEq per liter; blood pH 6.98; blood pCO<sub>2</sub> 13.5 mm of mercury; urine had a specific gravity of 1.028 with 4+ glucose and 4+ acetone. A throat culture later grew *Staphylococcus aureus* coagulase-positive, but two blood cultures drawn on admission remained negative.

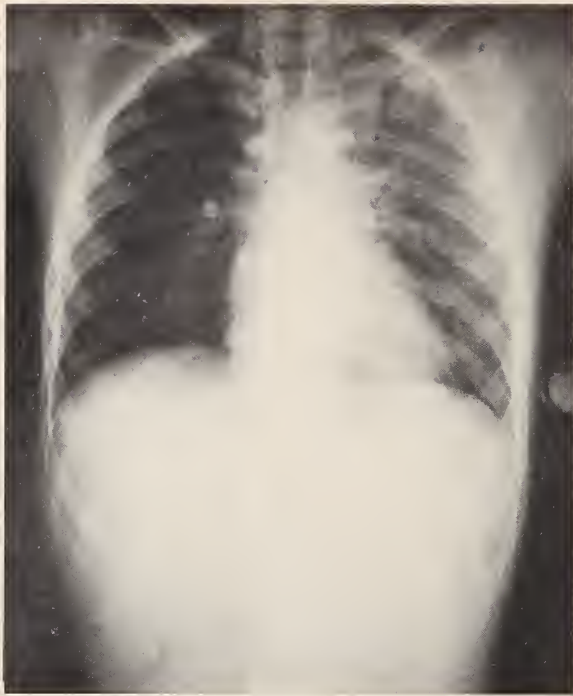
Initial treatment consisted of 40 units of regular insulin and 44 mEq of sodium bicarbonate intravenously. During the first eight hours of therapy, the patient received a total of 4300 ml of fluids, either Ringer's lactate or half-normal saline solution, containing 120 mEq of potassium chloride. A total of 270 units of regular insulin was administered at intervals during this period.

Additional management included nasogastric intubation with continuous gastric suction, seda-

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**Figure 1.**—X-ray film taken shortly after admission shows air in the mediastinum and pericardial sac.

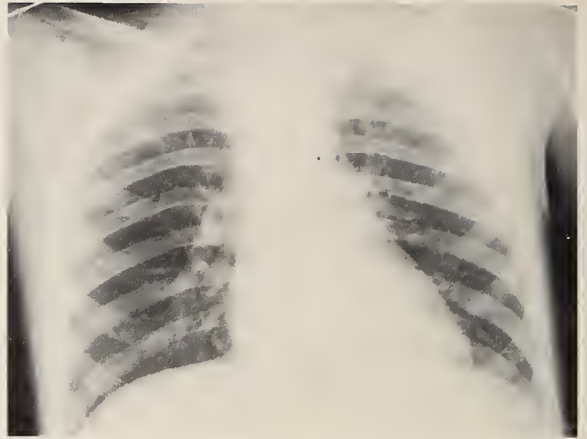
tion with frequent small doses of intravenous chlorthalidopoxide, and antibiotics.

An x-ray film of the chest taken shortly after admission revealed large amounts of air in the mediastinum and pericardial sac (Figure 1). There was no evidence of pulmonary infiltration or pneumothorax. A plain film of the abdomen showed no abnormality; in particular there was no free air beneath the diaphragm or retroperitoneal air lines.

Because of an abrupt temperature rise to 38.2° C (100.8° F) and a suspicion of infection with a gas-forming organism, the patient was treated with large doses of penicillin and kanamycin. The abdominal pain abated over the next 12 hours. An x-ray film the next day showed reduction of the mediastinal air (Figure 2). The following day the patient was afebrile. Complete restoration of blood chemical factors and electrolytes took 72 hours.

## Discussion

The occurrence of mediastinal emphysema (pneumomediastinum) during the course of diabetic ketoacidosis has not been appreciated until the past several years.<sup>1-4</sup> We were unaware of this at the time the patient was being managed,



**Figure 2.**—X-ray film the day after admission and following treatment with penicillin and kanamycin shows reduction of mediastinal air.

and the presence of air in the mediastinum reminded us of a recent report of diabetic ketoacidosis with pneumointestinalis secondary to bacterial invasion of the colon.<sup>5</sup> The rapid recovery of the patient, however, eliminated infection due to a gas-forming organism as the cause for the mediastinal emphysema.

The underlying causes of mediastinal emphysema are numerous and varied. The more common conditions associated with or leading to its appearance include mediastinal trauma, perforation of an abdominal viscus with leakage of air through the diaphragmatic orifices, atelectasis, and parturition. Conditions resulting in expiratory resistance, such as bronchial asthma, inhalation of foreign bodies, positive pressure therapy, and a variety of respiratory infectious diseases are also prime culprits.<sup>6-8</sup>

The pathogenetic mechanisms involved in the production of mediastinal air, according to the Macklins, begin with a pressure differential across the walls of the marginal alveoli leading to their rupture. Pulmonary interstitial emphysema ensues, air then dissects proximally by way of the connective tissue sheaths of the pulmonary blood vessels.<sup>9</sup>

Concerning the possible relationship of diabetic ketoacidosis to mediastinal emphysema, several observers have suggested that the retching and vomiting, so common in the ketotic patient, are responsible for the abrupt distention and tearing

of alveolar septae.<sup>3</sup> Others implicate the Kussmaul-type breathing itself.<sup>2</sup> It would be of interest to learn if this complication occurs also with other forms of metabolic acidosis with deep hyperventilation, such as acute salicylism. In any event it is apparent that an association between these two entities does exist.

Treatment directed toward the mediastinal emphysema *per se* is usually unnecessary. If tension occurs, incision above the suprasternal notch to allow air to escape or simple percutaneous puncture of the resultant supraclavicular subcutaneous emphysema suffices, although some authorities recommend mediastinotomy.<sup>8</sup>

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## A HOMESPUN GAUGE OF NEUROLOGIC DEFICIT

"If you were on a desert island and had no laboratory tests or anything else to use in examining young children for neurologic deficits, you could use a tape measure. I think that this is the single most under used and most valuable technique for evaluating deficit in children. . . .

"There are two ways you can use the information from a tape measure. First you can plot the head circumference on a chart. A study from Denver, which puts together all of the available data in the literature, shows that there is very little variation from one nationality or race group to another in terms of the normal head size. If you find, for example, that the head circumference deviates from the mean as much as two standard deviations, I think you've got important diagnostic information, especially in an infant who is behind developmentally, or experiencing seizures, or in whom you suspect central nervous system difficulties.

"An alternative way of using this information, one that I use regularly, is to simply obtain a normal head circumference measurement for boys and girls and put it in your wallet. . . . What we did in determining intracranial volume was to take a set of x-ray measurements and compare them with head circumference measurements; the degree of correlation was .985. That's why I think you really don't have to get fancy and you don't need the radiologist's evaluation of head size if you use the tape measure."

—PATRICK F. BRAY, M.D., Salt Lake City  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# LETTERS *to the Editor*

## Federal Health Insurance Now?—No

*To the Editor:* I have favored increased federal participation in health care provisions all my life, but I am appalled at the prospect that under various pressures a system of national health insurance may be prematurely enacted at this session of the Congress. To do so, with the present chaotically run system for the delivery of medical services prevailing, is to invite a mess that will make the present Medicare and Medicaid seem orderly.

The health of the people is a proper concern of government, for our national strength depends upon it. Support for the aged, for the indigent, for the veterans, for state and federal employees, in meeting their health needs is now almost universally accepted as an obligation of the government. This is not the question. The question is how can this be done in the most efficient and economical manner consistent with maintaining high quality of care.

This cannot be done without a profound reorganization of the delivery system. This reorganization should take the form of hospital-based multi-specialty group practice with capitation prepayment by an organized group of beneficiaries who “belong” to the center as they belong to their church or union. I have described this in numerous articles (“Provision of Medical Services,” *New England Journal of Medicine*; “Hospital-based Group Practice,” *Hospital*; “The Community

Health Facility,” *International Conference on Group Practice*, 1970) and will not go into detail again. But, briefly, it consists of a community health facility—an intensive care hospital core, “a going in,” “a going out” facility, a facility for “in-and-out” care for mental illness, a facility for alcoholism, for extended care and for research. It should be staffed by a hospital-based and domiciled multi-specialty group practice clinic with ample use of paramedical personnel. Each facility should serve about 250,000 to 300,000 people. The facility should be supported by capitation payments—one for hospital services and a separate one for medical services. Built-in assurance against over-utilization should be provided by enabling the group practice clinic to profit by any economies achieved in the hospitalization. A quality control commission on which the patients have representation should be established to insure adequate and high quality care.

These facilities should have reciprocal arrangements with each other to enable members of one to be treated in another. The plan being presently worked out by University of California, San Francisco, and the San Francisco County Medical Society should be applied everywhere on a reciprocal basis.

The role of the federal government should be the provision of grants or loans of funds needed to establish such centers, to purchasing participating memberships for Medicare, Medicaid, veterans, and other government wards, and to establishing standards to be followed.

This kind of reorganization must precede any federal health insurance. And if this plan works—three prototypes should be immediately established to test the plan—one in a “core” area in a

city, one in a typical suburb, and one in a rural area. If such locally controlled comprehensive prepayment plans are successful no federal insurance will ever be needed.

It would be a disastrous mistake to impose a vast federal insurance system on this country. It would be really like building a magnificent train with no tracks on which it could run.

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## Post-Transfusion Hepatitis

*To the Editor:* The question of litigation arising out of a patient's developing post-transfusion hepatitis should be re-examined for many reasons.

First, the numbers of patients who develop post-transfusion hepatitis will be about 1 in 33 transfused, when the blood from a volunteer population is contaminated with as much as 44 percent of blood from prison donors. The numbers of patients with transfusion hepatitis, under these circumstances, who will be able to show disability or who will die of this disease, will be approximately 0.9 percent of the total transfused. If one considers only volunteer donors, we experience one case among every 278 patients, and about one serious or fatal case among every 1000 patients transfused.<sup>1</sup>

Second, the use of commercial blood carries a risk of causing transfusion hepatitis that is 10 to 70 times greater than when blood from volunteer donors is used.<sup>2</sup> Our 1964 California laws<sup>3</sup> erroneously assume that the bloods from all populations carry the same risk.

Third, it is not possible in most instances for the doctor to know if the blood his patient is about to receive is from a high or low risk population.<sup>4</sup>

Fourth, the patient, who brings in his volunteer donors in advance, has no assurance that the blood he receives will be from volunteers.<sup>5</sup>

Fifth, the Au antigen test, unless vastly improved, will detect only about 25 percent of infectious bloods.<sup>6</sup> Since the average patient receives 3.4 units (four units) of blood, three out of four potentially infectious bloods will escape detection and be used clinically; our present attack rate will be unchanged.

Sixth, 90 percent of post-transfusion hepatitis from blood can be traced to the use of commercial or prison blood.<sup>7</sup> The elimination of the use of these donors would be of most help to reduce transfusion hepatitis to a minimum, until a test of greater accuracy can be developed to detect the infectious carrier.

We can not develop a reliable national all-volunteer blood program as long as blood insurance programs are permitted to exist, or as long as commercial blood is a part of a blood bank operation functioning under the euphemism of "not for profit." This is an important matter to the patient's health.

In Western Europe and the Western Hemisphere, it is only in the United States that the unbridled use of commercial blood continues. In our system of economies, price relates regularly to quality. Commercial blood seems to be the one conspicuous exception.<sup>8</sup>

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## The Medi-Cal Cuts

*To the Editor:* It is hard for me to understand the weeping and wailing of many California doctors because of the recent Medi-Cal cuts.

If you choose to deal with a crocodile, don't be surprised if you lose an extremity.

To me the shame is that a majority of doctors couldn't resist a few easy dollars and quickly jumped aboard the socialistic Medi-Cal scheme.

FRED L. GREER, M.D.

*Wittier*



## Percival's Medical Ethics: Promise and Problems

CHAUNCEY D. LEAKE, *San Francisco*

THE PRACTICE OF PROFESSIONAL MEDICINE has been regulated both by external social forces and by internal guidance. Even as early as four millenia ago, medical practice in the vast Assyrian empire was brought under social control by the tough Code of Hammurabi. This was enforced on the basis of "an eye for an eye," and set the pattern for malpractice suits.

Since then many cultures have established legal regulations for assuring competence by medical practitioners, usually on the principle of license to practice. This was formalized by Roger II of Sicily about 1140 A.D., and enlarged by his grandson, the liberal Frederick II of the Holy Roman Empire, in 1224 A.D. An examination was required after five years of study. Licensees were to treat the poor without fee, to visit the sick daily and to avoid collusion with apothecaries. Similar statutes were later enacted in Spain and Germany. In England, royal charters in the sixteenth century authorized licensure of physicians and surgeons. This system spread into all countries. License to practice is commonly to be revoked on evidence of incompetence or felony. Thus good moral character on the part of medical practitioners is implied in medical licensure under the authority of the state.

More significant in promoting medical competence and morality has been the precept and example of distinguished physicians. Still influential are the Hippocratic *Oath*, *Law*, *Precepts* and *Decorum* from ancient Greece. All the great humanistic physicians and surgeons from Hippocrates to Osler and Schweitzer have reiterated and emphasized the high idealism expected of medical men in actual practice.

Most influential of medical deontologists has been Thomas Percival (1740-1804) of Manchester, England. To appreciate his endeavor it is

necessary to understand the social organization of the health professions in eighteenth century England.

First there were the physicians, gentlemen born of landed families with independent incomes. They attended the universities (Oxford or Cambridge) and received an M.D. degree. Although they disdained work, they condescended to help sick people with advice, recommending surgical operation or giving a prescription as might be appropriate. They saw patients in their homes and would never ask a fee. The custom grew of patients' leaving a gold guinea on the hall table as they withdrew.

Then there were the surgeons, usually sons of workmen, who did not attend the universities, who did not hold an M.D. degree and who resented being called "doctor." Usually apprentice-trained, they were tough hard workers and they charged all they could. Usually their patients were referred to them by physicians.

The third group were the apothecaries, who were family oriented tradesmen. They were the first to be approached if one were sick. If the condition were mild, the pharmacist might sell an appropriate preparation. But if the situation seemed to be more serious, he would refer the sick person to a physician. If the latter gave the patient a prescription, this was, in effect, an order on the druggist to be filled exactly as written.

This neat arrangement began to be disturbed with the growing industrial revolution. People moved into the cities hoping for quick money by working in the mills. They were cruelly exploited. Work was hard, wages low and living conditions appalling. There was much sickness, squalor and misery. Mill towns, such as Manchester, had to provide hospitals for the indigent sick. Problems arose regarding the management of the hospitals. Physicians, surgeons and apothecaries jockeyed for positions of prestige and power. It was a mess.

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It was in an effort to correct this unsatisfactory situation that Percival began to propose a set of guidelines for the physicians, surgeons and apothecaries, defining their responsibilities and relationships, and proposing rules of etiquette to control their conduct. His effort was directed primarily to the Manchester Infirmary which he had helped to organize. His rules for decent relationships between physicians, surgeons and apothecaries were long discussed before finally being published in 1804, just before his death. Many English and Scottish hospitals adopted these rules, and they became widely recognized.

John Brown (1810-1882), the genial physician-essayist of Edinburgh, said, in his *Excursus Ethicus* (1861), "Dr. Percival's *Ethics* is a classical book in its best sense: sensible, sound, temperate, clear thoughts conveyed in natural, clear, persuasive language." Percival was persuaded to call his work "Medical Ethics." As Brown says, this was "somewhat of a blunder." The book is more concerned with etiquette than with ethics, as I tried to show when I edited an edition of it in 1927. According to Brown, "The Duties of Physicians' would have been less pedantic and more correct and homely." It is precisely this confusion between mere etiquette and fundamental ethics that has caused so much trouble among members of the health professions, and with people generally.

Percival's *Code of Medical Ethics* was particularly influential in the United States. Frontier conditions with poor communication and much sickness led to the formation of many medical schools in an effort to supply needed local medical service. Almost all were unsatisfactory. Medical education and medical practice deteriorated. Samuel Brown (1769-1830), a high-minded Scottish teacher at Transylvania Medical School, Lexington, Kentucky, thought the unsatisfactory condition could be improved by organizing the better trained medical men into a society devoted to worthy standards of medical practice. Unfortunately it was a secret society, The Kappa Lambda Society of Aesculapius. Organized about 1819, it soon had chapters in all major cities in the United States and published 12 volumes of *The North American Medical and Surgical Journal*. It adopted Percival's Code as its guide to conduct. Its members, however, took advantage of organization to get preferential appointments to hospitals and schools, and resent-

ment grew against it. It apparently closed about 1839.

The same poor conditions in medical education and practice continued. In 1846, Nathan Smith Davis (1817-1904) began the organization of the American Medical Association, the avowed purposes of which were to promote and maintain worthy standards of medical education and practice. At its first meeting in 1847, it adopted Percival's Code as the basis for its official "Code of Ethics," departure from the rules of which would make a member liable to suspension or expulsion. Local societies carried the burden of enforcement.

Difficulties gradually developed over strict literal interpretation of the rules. Proper *medicos* were not supposed to have anything to do with quacks or anyone trained outside the regular professional schools. By the latter part of the 19th century, the problem of consultation with "homeopaths" became serious. Generally the "homeopaths" were successful, largely as a result of their gentleness and avoidance of drastic remedies. Although their theoretical ideas, as derived from C. F. S. Hahnemann (1755-1843) were unsound, they succeeded in practice in finally getting rid of the excessive bleeding, purging, vomiting and sweating which characterized the regimen of the humoral Galenists well into the nineteenth century. The ridiculously small doses of homeopathic drugs really had neither effectiveness nor toxicity, and, practically, the "homeopathic" physicians rediscovered unwittingly the Hippocratic principle of the *vis medicatrix naturae*. Also they were skillful surgeons.

The dispute over consultation with "homeopaths" was enough to split the New York State Medical Society. There were many self-righteous writings on "medical ethics," and the confusion between mere etiquette and real ethical theory grew. A partial solution occurred when William Henry Welch (1850-1934), the highly respected pathologist of the Johns Hopkins University in Baltimore, was successful in persuading the American Medical Association at its New Orleans meeting in 1903 to abandon entirely a "Code of Ethics," with its often conflicting rules, and to use instead a simple set of guidelines as "Principles of Medical Ethics" by which to judge socially acceptable behavior on the part of medical practitioners. These "Principles" were fur-



ther simplified in 1957. However, a difficulty continued in the use of the word "ethics" when really merely etiquette was meant.

The situation came into focus with the appearance of Joseph Fletcher's *Medicine and Morals* (Princeton, 1954). This bravely tackled the sticky problems of birth control, abortion, euthanasia, the right of a patient to die, the right of a patient to know the truth, and human experimentation. These are ethical problems and not merely matters of acceptable social conduct, or etiquette. The distinction may seem to be trivial. Yet ethical problems involve the complications of long debated general ethical theories, while etiquette is chiefly a matter of local social norms.

The Nuremberg trials, following World War II, focused attention on the moral questions of human experimentation, and resulted in the general acceptance of the Geneva modification of the ancient Hippocratic Oath. The difficulties are still being debated. On several occasions I tried to show the importance of considering the various ethical theories (some thirty significantly formulated\*) in relation to current medical problems, such as in the mood and behavior of the various persons involved in organ transplantation.

The trouble is that so few people realize the extent of variation and of conflict between the many ethical theories. Many of us profess a conventional Judeo-Christian ethic without appreciating its implications, and go on to practice a frank hedonism. Platonic social idealism, implied as the ethical standard by the health professions, affirms that the goal of living is social welfare, even at self-sacrifice. This is a tribal ethic basically, but Jesus extended it to include all humanity. Opposed to this is hedonism, maintaining that the purpose of one's life is to get as much personal pleasure out of it as possible.

The harmony ethic, suggested by Buddha, Confucius and Aristotle, attempts to compromise the two contradictory ethics of social idealism and hedonism. A more intellectual compromise was proposed by English empiricists under the term of "utilitarianism." This sets the standard of conduct on the basis of the "greatest good for the greatest number," the characteristic ethic of administrators. The practical Americans pro-

posed a pragmatic ethic—conduct based on experience and experiment: what works is good. This is the distinguishing, if subconscious, ethic of professional people, such as engineers, lawyers, and members of the health professions.

Consider, then, the problem in a kidney transplant, which is becoming modified with dialysis and post-mortem technique. In the classical transplant situation, the conscious donor is motivated altruistically, at self-sacrifice to do for another to enhance the social welfare; the recipient is activated by frank hedonism to live and to enjoy more life; the health professionals are pragmatically oriented in the effort to make the operation a "success," and the hospital administrative staff is guided by utilitarian standards. In such circumstances there may be much misunderstanding. No set of rules, such as embodied in a "Code of Ethics," can resolve the potential difficulty, since each situation is different, as are the personalities. In many cases, some understanding may be achieved by honest conference, in which all principal participants take part along with an intelligent and wise lawyer, clergyman and psychologist. Yet even if honest agreement is reached, the situation may change: the donor may regret the sacrifice, the recipient may develop a guilt complex, and the operation cannot be expected to be successful indefinitely even if auto-immune reactions are controlled.

## In Prospect

It seems to be the part of wisdom to examine critically the moral problems of the health professions in relation to the well formulated theories of ethics. We have progressed over the centuries from various aspects of social and self-regulation of our health professions, and we have tried formal guidelines to socially acceptable behavior. Still wanting is the professional technique of self-analysis by which individual and social needs may be understood, and channelled into conduct beneficial to all. Perhaps our increasing knowledge of the ways our complicated brains work may help. Already we are learning about how the chemical reactions within our limbic system and hypothalamic cells centers drive us to seek satisfactions, conditioned as they be in multitudinous ways, toward self and species preservation.

\*Ann NY Acad Sci, 169:388-396, Jan 21, 1970

# Multiphasic Testing, 1971

A Socio-Economic Report of the Bureau of Research and  
Planning, California Medical Association

RECENT YEARS have witnessed an increasing number of multiphasic health testing programs in a variety of settings, including hospitals, group practices, and neighborhood health centers, as well as independent settings physically detached from any other segment of the health services delivery system. As such programs have multiplied, important changes have occurred both in the technologic aspects and in the role which the programs and, indeed, the entire concept of multiphasic testing play with respect to the provision of health services in contemporary society.

An abundance of literature has been addressed to various and specific aspects of this broad subject. Drawing on the wealth of published information, as well as inquiries made of program sponsors, this *Report* attempts to provide a broad overview of the subject.

## *Background*

The concept of health screening is not a new phenomenon to the United States' health care system. Shortly after World War II, screening programs were established by state health departments for the detection of tuberculosis and syphilis. As these programs began to demonstrate their values in detecting disease processes, other tests were added to the original limited-purpose screening effort and multiple screening was envisioned as the next step in a natural progression of events. Although many in the medical community were initially unprepared to accept or did not recognize the need for multiple screening, the

concept continued to be employed in industrial settings and by local public health and voluntary health agency organizations, as well as by some large group practices.

The most widely publicized effort in recent years has been that of the Kaiser-Permanente Health Plan; its program has made Kaiser a model for what has been referred to as "the second generation" of multiphasic testing.\* According to Plan spokesmen, a complete evaluation of that program's effectiveness will not be possible for several years. Nevertheless, the concept of multiphasic testing has increasingly attracted the attention of individuals and organizations who see such a program as a valuable adjunct to services already being made available and one which warrants incorporation into programs of medical care.

A basic type of multiphasic testing includes a self-administered medical history, a series of anthropometric procedures such as height and weight measurements, and a battery of laboratory tests. Such screening usually takes from one to three hours, excluding the follow-up visit with a physician. Initially, the testing process relies heavily on ancillary and clerical personnel, automated equipment and, in many instances, computers, while physician involvement is kept at a minimum.

## *Potential Benefits of Multiphasic Testing*

The value of presymptomatic diagnosis or preventive health care is based on the hypothesis that

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\*Recent literature suggests that the term "multiphasic testing" is more appropriate than the term "multiphasic screening," although the two are used interchangeably. In this *Report*, the former has been used for purposes of consistency.



discovery and treatment at a stage when the disease is still latent or subclinical creates the best possibility of arresting or even reversing the disease process. Essentially, then, multiphasic techniques are designed to identify the healthy appearing, presymptomatic person who in fact possesses signs or symptoms which require further investigation. Conceptually analogous, of course, are the principles of periodic checkups for pregnant women, well-baby care, and prophylactic dental visits. There is also the far broader and more recently stated concept that the role of multiphasic testing transcends merely the early detection of disease, where its value is still questionable, in order to meet the increasing demand for health checkups and health appraisals as the definition of the term "medical care as a right" becomes increasingly broad.<sup>1</sup>

It should be emphasized that, even though multiphasic testing may give early warning of a defect, it is neither intended nor expected by knowledgeable observers to replace a physician's diagnosis. Ideally, test results are utilized by the patient's physician as an aid in conducting a physical examination, making a diagnosis or prescribing treatment.

Multiphasic testing also affords an excellent opportunity for health education. By taking part in the screening process, people may tend to become receptive to learning about various indications of diseases (e.g., obesity, high blood pressure), the nature of common chronic illnesses such as diabetes, the proper care of eyes at middle age, and similar subjects. Other secondary purposes of multiphasic testing may include the accumulation of information for epidemiological research and a further education of the medical profession concerning early manifestations of chronic diseases.<sup>2</sup>

Despite a multiplicity of problems, potential benefits that have been attributed to multiphasic testing by its proponents can be quite significant. Of particular importance are the following:

1. An increase in the quantity and quality of medical records;
2. Accumulation of personal data that can serve as a baseline for comparison with data from future health exams (this is possible only if the agency or physician assumes responsibility for continuity of patients' records);
3. Reduction in the costs of health care to the individual patient and to society by decreasing

hospital inpatient activity and by avoiding expensive complications with early intervention in the disease process;

4. Maximization of physician time which tends to have the effect of reducing the shortage of physicians by utilizing technical aids and ancillary personnel;

5. Expansion of epidemiological knowledge.

In addition to these specific benefits, advocates of multiphasic testing have as an over-all goal a decrease in mortality and morbidity rates among examinees. They are hopeful that they will soon have information to corroborate these proposed benefits. At this time, however, insufficient evidence has been accumulated. (A discussion of problem areas in multiphasic testing may be found later in this *Report*.)

### *Tests Included in Multiphasic Programs*

The tests included in any given multiphasic testing program may vary substantially, depending on such things as cost considerations and the kind of population being tested. The following list of tests is a composite program consisting of tests being done by a minimum of five out of seven major multiphasic testing programs throughout the country. The list consists of 37 tests.

Although many critics of the multiphasic programs maintain that there is no cost-justification for many of the tests being done, the number of tests being included in programs is large and growing rapidly. Among the many possibilities suggested for future inclusion are tests to detect various kinds of cancer, tests to determine the extent and severity of serious mental illness and further testing procedures for the pregnant woman and fetus, including tests for rubella.

Understandably, the development of any multiphasic testing program requires extensive planning and organization. In an effort to determine optimal guidelines to assist organizations in the process of developing a testing program, the National Center for Health Services Research and Development held a national conference on automated multiphasic health testing and services which brought together recognized experts in the field. The proceedings from this conference, which space limitations in this *Report* preclude from being discussed, have recently been published and can serve as an invaluable reference to the interested reader.<sup>3</sup>

### A Composite Multiphasic Testing Program\*

Anthropometry: 1. Height and weight	C. Glucose Tolerance	Ophthalmology: 1. Visual acuity 2. Tonometry
Audiometry	D. Hematology: 1. Hematocrit 2. Hemoglobin 3. Red blood cell count 4. White blood cell count	Questionnaire: 1. Present medical history 2. Past medical history
Cardiovascular Measurements: 1. Blood pressure 2. ECG 3. Pulse	E. Enzymes: 1. LDH 2. Alkaline phosphatase 3. Transaminase (SGOT)	Radiology: 1. Chest x-ray
Clinical Laboratory Procedures: A. Blood Chemistry 1. Bilirubin 2. Calcium 3. Cholesterol 4. Protein, total 5. Protein, albumin 6. Phosphorus, inorganic 7. Urea nitrogen 8. Uric acid	F. Syphilis Serology	Spirometry: 1. Forced vital capacity (total) 2. Forced expiratory volume (1 second)
B. Blood Group	G. Urine Tests: 1. pH 2. Glucose 3. Protein 4. Blood 5. Ketones 6. Bacteriuria culture	Uterine Cervical Cytology (Pap smear, female)

\*The programs from which this list was compiled include: Kaiser-Permanente, Brookdale Hospital Center, Tennessee Regional Medical Program, Tulane University School of Medicine, Milwaukee City Health Department, Rhode Island State Health Department, and IBM Evaluation Program.

### *On-going Multiphasic Testing Programs in California*

Currently there are at least a dozen multiphasic testing programs functioning in California.\* Brief descriptions of these programs are presented below, along with Table 1 which provides information about the programs' medical directors, locations, sponsorships, clientele, and fees. Space limitations preclude full discussion of each program; the descriptions can merely provide some basic information about each program and, when appropriate, indicate any distinctive characteristics.

#### **Automated Multitest Medical Laboratory**

In March 1970, the Palo Alto Clinic opened its multiphasic testing center. The testing facilities were built in cooperation with Automated Medical Laboratories International (AML).

The AML facilities are designed in such a manner that the patient remains in a three-sided cubicle while a central rotating drum brings the testing devices to the patient rather than having the patient move from one station to another. Another distinguishing feature of this system is that one technician is assigned to each patient rather

than having the patient encounter a succession of technicians.<sup>4</sup>

The laboratory has six modular systems allowing a testing capacity of 84 patients per day. The testing costs each patient \$40 and takes approximately two hours of a patient's time. The facility is available only to persons referred by a physician.

#### **Cannery Workers' Health Checkup**

The California Cannery Workers' Health Check-up (also known as Health Testing Services, Inc.) originated as a benefit attained through collective bargaining between the Cannery Workers' Union and the California Food Processors in 1964. The program operates only during the canning season, from June to October. Within this limited time period, the testing facilities are transported to approximately 60 working sites in California and an average of 21,000 cannery workers are tested. The program began operation in 1967; it was continued in 1968 but from then on has operated on a biennial basis.

The testing facilities are contained in a mobile unit consisting of three vans. The facilities are staffed by a combination of professional and non-professional persons who are specifically oriented to interpret the program to the canning community and to be responsive to the screenees' level of health care acceptance, personal fears and misunderstandings, and cultural attitudes.<sup>5</sup>

\*Programs listed represent those about which substantial descriptive information was available to the authors. For a complete listing of on-going programs in California, see the *Multiphasic Screening and Automated Health Evaluation Programs Directory* published by Multiphasic Screening Newsletter. The inclusion of specific programs in this Report does not constitute their endorsement or approval by the California Medical Association.



TABLE 1.—On-Going Multiphasic Testing Programs in California, as of November 1970

Program	Medical Director	Location	Sponsorship	To whom available	Fee
Automated Multitest Labs	Hilliard Estes, M.D.	Palo Alto	Private corporation in cooperation with Palo Alto Clinic	M.D. referrals	\$40.00
Cannery Workers Health Checkup	(a)	Mobile Unit	Union and Management Health and Welfare Fund	Union members	(b)
Comprehensive Health Testing Labs, Inc.	Robert Morris, M.D.	San Francisco	Private corporation	Employee groups; M.D. referrals	\$15-65
East Bay Screening Center (Alta Bates)	David Singman, M.D.	Berkeley	Alta Bates Hospital with Medidata Sciences, Inc.	M.D. referrals	\$40.00
East Palo Alto Community Health Center	Eugene Patterson, M.D.	East Palo Alto	Regional Medical Program	Area residents	(b)
Health Evaluation Systems, Inc.	Lawrence Taylor, M.D.	Los Angeles, West Covina, San Diego, Highland Park	Private corporation	M.D. referrals	\$25-50
InterHealth	Charles Ross, M.D.	San Diego	Private corporation	M.D. referrals	\$55.00
Kaiser Foundation	Morris Collen, M.D.	Oakland, San Francisco	Prepaid group practice plan	Plan subscribers; Non-member M.D. referrals	0-\$3.50 \$30-40
Predictive Medicine Program (Retail Clerks 770)	W. C. Martin, M.D.	Los Angeles	Retail Clerks Unions and Food Employers Benefit Fund	Members of union local	(b)
St. Francis Multiphasic Program	Lawrence Carr, M.D.	San Francisco	Hospital	M.D. referrals	\$50.00
St. Mary's Health Appraisal Program	James Diestel, M.D.	San Francisco	Hospital	M.D. referrals	\$50.00
San Joaquin Health Checkup	Virgil Gianelli, M.D.	Stockton	County Medical Society with Regional Medical Program funding	Migrant workers; urban poverty groups	(b)

(a) This program has a consultant board for all projects. The board currently includes: Gerson Biskind, M.D., William Kieferdorf, M.D. Harold Rosenblum, M.D., Samuel Sherman, M.D., and Earl Stern, M.D.

(b) Free to qualified persons.

The follow-up visit has been a major concern in this program. During the first season of testing, one-third of the cannery workers did not have an established family physician. The administrators of the Health Checkup, with the help of county medical societies, were able to alleviate this problem to the extent that only 11 percent of the examinees were unable to name a personal physician when the program was repeated in 1968.

### Comprehensive Health Testing Labs, Inc.

Comprehensive Health Testing Labs, a private corporation, began operating in San Francisco in the latter part of 1969. It provides multiphasic testing to employee groups and to patients referred by a physician.

CHTL offers several basic test programs and provides open-ended selection capabilities so as to suit the multiphasic test panel to specific needs of groups of employer-union clients or physicians. The programs include the Comprehensive Multiphasic Laboratory Examination (\$65), the Physician's Preoperative Multiphasic Panel (\$46), and others sealed down in cost and scope.

This screening center is designed to handle fifty to sixty patients per day, using specially trained paramedical personnel who perform nearly all the tests for each patient in a private, specially equipped examining room. Although there is presently only one testing site, plans exist for modular multiphasic health screening centers. These modular laboratories could keep their costs at a minimum by utilizing the automated equipment and central computer bank of the parent laboratory.

### East Bay Health Screening Center

The East Bay Health Screening Center is a part of the Alta Bates Community Hospital in Berkeley. The program first began accepting physician-referred patients in January 1970 and was one of the first screening programs to operate in a private community hospital for utilization by private physicians. The facility was designed by Medidata Sciences, a division of C. D. Searle and Company, which seeks to place such complete testing units in other hospitals throughout the country.

A significant feature of this program is that the medical history is taken by means of a computer console which can pose as many as 320 questions on a video screen. The patient's response is relayed to the computer through a push-button control. Since each series of questions is dependent

upon the patient's response to previous questions, only necessary questions are asked.

The screening process includes approximately 40 tests and the medical history. The cost to each patient is \$40. The center has a capacity of up to 80 patients per day. Although the center has not been in operation long enough for its utilization by community physicians to be effectively determined, a recent study shows that approximately 75 percent of the Alta Bates staff plan to use the services in their medical practices.<sup>6</sup>

### East Palo Alto-East Menlo Park Neighborhood Health Center

At the time this *Report* was prepared, the East Palo Alto Neighborhood Health Center indicated its plans to begin a multiphasic testing program in December 1970. The testing program will be underwritten entirely by federal funding provided through the California Committee on Regional Medical Programs for a one-year period.

The testing program will be a routine procedure in the Health Center's process of care. Test results will automatically be sent to the patient's physician at the Center; hence, a follow-up visit is assured. Plans for the testing program estimate that approximately 275 patients will be tested each month.

### Health Evaluation Systems, Inc.

Health Evaluation Systems opened their first screening center in West Covina in 1968. Since then, additional centers have been established in San Diego in 1969 and in Los Angeles and Highland Park in 1970. The centers are privately owned and are designed to test individual patients and employee or union groups.

In order to meet the fluctuating needs of both patients, the HES centers offer flexibility in the sequence of tests performed on any given patient or group. The cost of the testing for individual patients ranges from \$25 to \$50; each center has a capacity of 50 patients per day.

In the near future, HES plans to begin operating a master information system which will receive and process patient data supplied from HES centers throughout the nation. This information will allow patients' medical records to be tabulated and compared to the HES national file. This system will also allow a patient's medical record to follow him if he moves from one region to another.



## InterHealth Med-test Centers

InterHealth, a private corporation, is jointly owned by a large group of physicians and by Systems, Science and Software, a computer science and technology firm. The parent laboratory was opened in San Diego at Grossmont Medical Center in November 1970.

InterHealth plans to establish eight to ten satellite testing centers which will open at two- to three-month intervals according to patient demand. The central clinical laboratory and computer installation will process patient data from the respective testing centers.

Each testing center will have the capacity to test 30 to 40 physician-referred patients per day. A standard battery of tests costs a patient \$55 and requires approximately one hour of a patient's time. Should the physician wish to order specific additional tests, however, these too can be arranged for an additional charge.

## Kaiser Foundation Health Plan

Undoubtedly the best known and most emulated multiphasic testing program is that which has been operating through Kaiser Hospitals in Oakland and San Francisco since 1950. It was, however, not until 1964 that the program was revised to implement automated testing procedures. The testing is available both to Kaiser members and non-members; all patients, however, must have an appointment with a physician for a follow-up visit before they may participate in the multiphasic testing program.

Both testing centers have an average patient load of 2000 per month, based on a 40-hour week. Forty percent of those persons tested are over age 50; minors may participate in the program with written consent from their parents. According to their plan coverage the charge for multiphasic testing varies among members from no-charge to a maximum of \$3.50. The charge is \$30 for non-members with the exception of women aged 48 and over if they are to receive a mammography.

The Kaiser program is administered by having the examinee proceed to 20 different stations in a period of two to three hours. By the time the examinee has finished at Station 20, the "on line" computer processing of selected test results has been completed and necessary additional tests and appointments are arranged for the examinee. Simultaneously, the "off line" computer collates

and stores the remaining information (physician interpretation from the EKG, roentgenograms, and the retinal photograph; the remaining laboratory test reports; and the key-punched medical questionnaire form). When all of the final information has been received and stored, the computer produces a printed summary of test results and questionnaire responses.

Because their testing centers have been operating longer than most and because of their larger-than-average patient load, the Kaiser program is one of the few that have been able to publish meaningful data such as the incidence of and costs per positive finding. Some of these data are contained later in this *Report*. In the future it will be data such as these that will be necessary for assessing the actual worth of screening for the patient and the physician.

## Predictive Medicine Program (Retail Clerks Unions and Food Employers Benefit Fund)

The Predictive Medicine Program was established in Los Angeles by the Retail Clerks Local 770 and the Food Employers Benefit Fund for the purpose of giving union members and their dependents routine access to a medical examination which would include both physical and laboratory tests. This benefit, which is totally without charge, is in addition to the regular health plan which provides for a dual option of either the Kaiser Plan or an indemnity plan.

The program has been operating for nearly five years. Throughout this time, health education has been one of its major objectives. A nutritionist is stationed at one of the testing areas to discuss diet, exercise, smoking habits, and general hygiene with the patient.<sup>7</sup>

Special emphasis is also placed on the follow-up visit. Hence, a physician is employed by Predictive Medicine to insure a follow-up for those persons who do not either belong to the Kaiser Plan or have a personal physician.

## Saint Francis Multiphasic Physical Examination

St. Francis Hospital in San Francisco began operation of its multiphasic program in 1969. The program is on a smaller scale than most multiphasic testing programs in the State. It was designed entirely by members of the hospital staff

and is made available to patients of physicians on the staff. Using existing in-house facilities and equipment, the testing capacity is approximately five patients per day; at present, an average of five patients are tested each week. The charge for the testing procedure is \$50. To assure a follow-up visit, every patient must be referred by a physician.

### Saint Mary's Health Appraisal Program

In 1968 St. Mary's Hospital and Medical Center began its health appraisal program. This Multisystems testing program is available to patients of any physician and is restricted only insofar as all patients must have been referred by a physician. In addition to such referrals, one contract with a union health and welfare plan for testing its members is currently in existence.

The program was developed entirely by the hospital staff and utilizes existing facilities and equipment. The charge for the testing is \$50 per patient. At present, approximately five to six patients are tested each day; the program has the capacity to test 50 patients per day.

### San Joaquin Health Checkup

The San Joaquin Health Checkup was conceived by the San Joaquin County Medical Society and its foundation for Medical Care and is being funded federally through the California Committee on Regional Medical Programs. Funding originally became available in mid-1970, at which time the program began, and is guaranteed for a three-year period.

The health checkup is designed to bring preventive and continuing medical care to economically disadvantaged urban families and migrant workers in the area. The goal of the program is to test 3,000 persons annually for the next three years and, in this way, bring into the health care system those who might otherwise remain outside it.

Whenever possible, the program utilizes personnel and equipment used in the Cannery Workers' Health Checkup; thus, the testing facilities are housed in mobile vans. Tests for lung function, blood pressure, visual acuity, heart function, various x-rays, and blood and urine tests (and "Pap" tests for women) are carried out by a staff of bilingual physicians, registered nurses and technicians. The testing is free for qualified persons; the estimated cost per examinee is \$34.<sup>8</sup>

The San Joaquin Foundation for Medical Care plays a vital role in organizing the provision of necessary follow-up services for those persons not having an established relationship with a physician. Migrant camp residents are referred to existing camp clinics; urban residents are referred to the Pearl Sifford Clinic. Persons requiring services not provided by a clinic are referred to the County General Hospital on a special outpatient basis established within the framework of the outpatient department.

Although many of the programs described above have not yet published data on the cost of initiating and maintaining their multiphasic programs, a few testing centers have been operating long enough and on a large enough scale to provide such information. It is important to note the high initial cost of a testing program, since this should be a significant factor in evaluating the need for establishing more testing centers before those existing centers are utilized to capacity. The only factor that can offset the major expense of a screening program is capacity utilization.

A comparison of expenditures for establishing and operating screening programs is difficult because of (a) varying numbers of examinees, (b) varying numbers of tests performed and (c) different accounting techniques. There are other intrinsic differences peculiar to individual programs which make comparisons difficult. For example, although the East Bay Screening Center and the Kaiser program are both hospital-based, the latter operates on a much larger scale and has operated for a longer period of time. Furthermore, Kaiser is essentially a closed system and has been able to incorporate multiphasic testing into its over-all health care program, while the East Bay Screening Center is dependent upon outside physician referral and is itself "free standing." The Cannery Workers' program varies in other respects, being a mobile unit that operates discontinuously. Thus, the cost information presented below is somewhat limited in terms of providing a basis for meaningful comparisons.

Nevertheless, the data are in themselves of general informational value for persons considering the establishment of such a program or evaluating various existing programs. Again, space limitations in this *Report* preclude extensive discussion of costs of individual programs; for detailed information, the reader is directed to the source material cited.



**TABLE 2.—Operating Expenditures and Cost Per Examinee for the Cannery Workers' Health Checkup, 1968**

Component	Total	Cost Per Examinee
Trailer moving . . . . .	\$ 16,000	\$ 0.76
Field operation . . . . .	214,100	10.19
Field personnel . . . . .	177,200	8.44
Testing supplies . . . . .	28,100	1.34
Other field expenses . . . . .	8,800	.41
Professional contracts . . . . .	212,000	10.10
Data processing . . . . .	78,000	3.71
Central office . . . . .	244,200	11.67
Personnel . . . . .	162,900	7.82
Rent . . . . .	19,400	.92
Accounting and legal . . . . .	10,200	.48
Supplies and equipment . . . . .	35,600	1.69
Other . . . . .	16,100	.76
Travel . . . . .	11,000	.52
TOTAL . . . . .	\$775,300	\$36.95

### The East Bay Screening Center

A complete breakdown of expenditures by the Alta Bates Community Hospital on the establishment of the East Bay Screening Center is not available at present; however, some of their major expenditures include the following. Based on a patient load of 50 patients per day, the annual operating budget is estimated at \$437,000. Two major expenditures include \$100,000 for a furnished building in which to house the program and the cost of leasing the computer and testing equipment which is valued at \$350,000.<sup>6</sup>

### Cannery Workers' Health Checkup

The Cannery Workers' Health Checkup has published a summary of operating costs for 1968. These figures, along with the cost per examinee, are outlined in Table 2.

The total operating costs for 1968 amounted to \$775,300. Of this total annual cost, 31.6 percent (\$244,200) was spent on maintaining the central office. Other major expenses included the cost of field operations (\$214,100) and of professional contracts (\$212,000) which amounted to 27.6 and 27.3 percent, respectively, of the total annual cost.

Calculated from a total patient load of 20,990, the cost per examinee was \$36.95. However, it was estimated that the cost per examinee would be reduced to \$26.96 if the patient load were increased to 50,000 examinees who could be tested if the program were expanded to operate on a year-round basis.

Capitalization costs necessary to initiate the program totaled \$203,900. This included the cost

**TABLE 3.—Total and Per Unit Cost of the Kaiser-Permanente Multiphasic Testing Program, September 1967-August 1968**

Component	Total	Cost Per Examinee*
Direct costs . . . . .	\$585,249	\$12.34
Equipment depreciation . . . . .	54,557	1.15
Salaries and wages . . . . .	407,835	8.60
Supplies and equipment . . . . .	122,857	2.59
Allocable indirect costs . . . . .	91,964	1.94
Unallocable indirect costs . . . . .	333,724	7.04
Computer center and data processing . . . . .	213,318	4.50
Central staff . . . . .	120,406	2.54
TOTAL . . . . .	\$1,010,653	\$21.32

\*Based on a patient load of 47,404.

of equipment (\$186,400) as well as the cost of planning (\$17,500).<sup>5</sup>

### Kaiser-Permanente Multiphasic Testing

The Kaiser multiphasic program has reported operating costs for one year, from September 1967 to August 1968. Direct and indirect operating costs and the cost per examinee are outlined in Table 3. It is important to note that these figures were based on the operation of the screening centers in San Francisco and in Oakland.\*

The cost per examinee was calculated to be \$21.32 on the basis of 47,404 patients tested during that period. Direct costs, which included equipment depreciation, salaries and wages, and supplies and equipment, totaled \$585,249. These direct costs accounted for 57.9 percent of the total annual cost of \$1,010,653.

Indirect costs were separated into those expenses which could be allocated to specific aspects of the program and those which could not. Allocable indirect costs amounted to \$91,964, or 9.1 percent of the total annual cost, while unallocable indirect costs amounted to an additional \$333,724, or 33.0 percent of the total. The latter included the cost of the data processing (\$213,318) and of the central staff (\$120,406) which provided the administrative, instrumentation, systems, statistical and epidemiological personnel utilized in the program.<sup>9</sup>

### Dollar Cost Per Positive Test Finding

An additional and important type of information is that relating to the cost per positive find-

\*Similar cost information has been published for the Tulane Health Maintenance Project. (MacKintosh D, Krause G: Cost analysis of the developmental phase of an automated multiphasic health testing facility. Public Health Reports 85:685-689, August 1970.)

TABLE 4.—*Cost Per Positive Test in Kaiser-Permanente Program, 1967-68*

Test	All ages			Age 60 and over	
	Unit cost	Percent positive	Cost per positive finding	Percent positive	Cost per positive finding
Mammography	\$4.90	1.2%*	\$408.00*	1.4%	\$350.00
Electrocardiography	1.02	17.3	5.90	31.5	3.20
Tonometry	.55	0.3	183.00	0.5	110.00
Chest x-ray film	.46	7.4	6.20	19.2	2.40
Blood pressure	.42	4.1	10.20	11.5	3.65
Respirometry	.31	2.2	14.10	2.7	11.50
Visual acuity	.29	15.8	1.85	26.3	1.10
Audiometry	.25	16.2	1.55	36.4	.70
Ankle reflex	.24	1.5	16.00	1.6	15.00
Hemoglobin (men)	.42	3.1	13.55	5.6	7.50
Hemoglobin (women)	.42	10.3	4.10	5.5	7.60
White cell count	.42	2.2	19.10	1.7	24.70
Serum glucose (1 hour)	.75	5.7	13.15	8.3	9.05
Serum cholesterol	.29	2.4	12.15	3.0	9.70
Serum uric acid	.29	4.5	6.40	6.0	4.80
Serum albumin	.29	0.3	96.70	0.4	72.50
Serum total protein	.29	4.0	7.25	3.9	7.45
Serum calcium	.29	1.3	22.30	1.5	19.30
Serum creatinine	.29	1.4	20.70	2.7	10.70
Serum transaminase	.29	4.2	6.90	4.5	6.45
VDRL	.16	1.5	10.65	2.3	6.45
Urine culture (men)	.20	0.4	50.00	1.0	20.00
Urine culture (women)	.20	3.3	6.05	4.0	5.00
Urine glucose	.18	8.2	2.20	7.3	2.50
Urine protein	.18	6.4	2.80	7.0	2.60

\*Women 50 years of age or older.

ing in testing programs. As yet, Kaiser-Permanente is the only California program to have compiled extensive data of this nature. Their information describes the cost per positive test, based on 44,663 multiphasic examinations performed between September 1, 1967 and August 31, 1968. As can be seen in Table 4, the cost per positive case ranged from \$1.55 per positive audiogram to \$408.00 per positive mammogram. Obviously, this type of unit cost is contingent on the characteristics of the population tested. Nevertheless, the data provide an important tool for evaluating the cost-effectiveness of multiphasic testing.

The unit cost for mammography, including interpretation of x-rays by a radiologist, was \$4.90. Mammograms were provided only to women over age 50. The incidence of positive cases was 1.2 percent and cost per positive case, \$408.00. For women 60 years of age or older, the positive incidence increased to 1.4 percent, thus decreasing the cost per positive case to \$350.00. In his recent article, Garfield notes that, if 500 women were tested, these findings could alternatively be

stated in the following manner: "It cost \$4.00 each to assure 499 women there is no evidence of breast cancer by mammography and \$4.00 to detect one cancer that through early surgery may have a better prognosis."<sup>1</sup>

Tonometry, with a low over-all unit cost, also had a relatively high cost of \$183 per positive case, since the positive incidence was a very low 0.3 percent for all persons tested. Among the age group 60 and over, however, the 0.5 percent with positive findings lowered the cost to \$110 per positive case.

It is interesting to note that the unit cost for an electrocardiogram was one of the highest (\$1.02); however, the high incidence of positive findings (17.3 percent) resulted in a relatively low cost per positive case (\$5.90). If only those persons 60 years of age or older had been tested, the cost per positive case would have been reduced to \$3.20. The age relationship is even more dramatic in blood pressure testing, in which the cost per positive finding of persons under 40 was \$105.00, while the cost for persons 60 and over was \$3.65.<sup>10</sup>



## *Problems and Controversies*

### *About Multiphasic Testing*

Many physicians are apprehensive about accepting multiphasic testing as an integral part of their routine practices. Their apprehension is based not only on the belief that multiphasic testing represents an impersonal, assembly-line type of medical care, but also on some of the problems of testing such as the incidence of false positives and false negatives. It is understandable, furthermore, that the physician will not readily accept multiphasic testing programs if the results do not justify the costs or if they provide the patient with a false sense of security regarding his health status.

Some physicians who have worked with testing programs cite false positives as their main criticism. They would prefer spending their time with a person clearly in need of specific diagnostic or therapeutic procedures, rather than assuaging the fears of a patient whose testing falsely indicates a positive result. Although a certain percentage of false positives is unavoidable, a physician burdened with invalid test results is bound to question the worth of testing.

Kaiser-Permanente handles the problem of false positives by considering the nature of the disease being tested for in each testing procedure. With a disease such as tuberculosis, they set the level so that anyone with a questionable x-ray is called back. They are willing to risk false positives on conditions that are potentially important to the patient. However, with less serious conditions, they raise the testing levels, knowing that some mild cases will be overlooked until the following year.<sup>11</sup>

Test results which are false negatives create an equally important problem. If a patient does not understand that testing results alone are not a complete and sufficient diagnostic survey, false negatives may give him an inaccurate sense of security about his health. It is also important that examinees do not consider the test results to have predictive value concerning possible health problems in the future.

An important objective of most testing programs is to improve the definition of normal values. Efforts are being made to include more parameters in defining what is normal and what is not, and to individualize evaluations by including and adjusting for such factors as biological rhythms (year, month, day) and drugs being

taken. There remains a considerable amount of concern in the medical community with respect to the establishment of normal ranges.

Another area in question is the effect that testing will have in relation to the medical manpower and facilities shortage. Many proponents of testing argue that one of its benefits will be to alleviate the physician shortage by making more effective use of ancillary personnel. As yet, there is no evidence either to refute or to affirm this hypothesis. Furthermore, since another proposed benefit of testing is that it will be able to reach larger portions of the population, it is possible to anticipate that the immediate effect of any increase in the amount of testing done will be to increase the strain on all types of manpower and facilities, most of which are already in short supply. The very existence of programs, especially those available at no charge, cannot but increase the number of the "worried well" who utilize facilities and personnel. Although this problem may prove to be short-range in nature, it is an understandable concern to those who are called upon to provide these additional services.

The effect of multiphasic testing on the utilization of health care facilities and personnel will probably be a function of what segment of the population being so tested has already been undergoing some sort of routine screening or annual health examinations. Additionally, one must also take into account not only the manpower and facilities used in the testing programs, but also the resources utilized in the follow-up visits or the possible hospitalization necessary to treat the conditions detected in a testing program. Optimally, this whole dilemma will be resolved with allocation of scarce and expensive resources to the area where the least input produces the greatest results, within the limitation of providing adequate resource allocation to areas of immediate or critical need.

The success of a multiphasic program is dependent on the referral to and follow-up by physicians both within and outside of the testing program. Persons organizing multiphasic programs are aware of the importance of the follow-up visit and will usually make intensive efforts to effect patient-physician follow-up contact.

Nevertheless, there are follow-up problems which are difficult to control under an open system, such as the following:

1. the examinee does not go to a physician as he was directed;
2. the patient does not follow the course of treatment outlined by the physician; or
3. the examinee has no family or personal physician.

Unfortunately, while testing holds the greatest potential for helping to alleviate health problems among the urban poverty population, it is this group with its high illness rates and physician shortages that seems to be most vulnerable to failure in the follow-up process.<sup>2</sup> Even among other groups, health care coverage which does not provide reimbursement for follow-up services can constitute an effective barrier to this important aspect of testing programs.

The concern with the follow-up visit is relatively less critical in closed systems such as Kaiser than in other settings. In general, however, testing programs currently being developed are designed to insure a follow-up by requiring physician referral to a participant in the testing program or, as in the case of San Joaquin Health Checkup, the program assures physician-patient contact through arrangements with county medical societies, local health clinics, or county hospitals. Also, those programs based solely on physician referrals have a built-in follow-up mechanism.

There is one final area of concern on the part of many physicians. It has been observed that in many instances early detection of abnormalities serves little useful purpose in the provision of medical care, since no immediate measures for dealing with many of these abnormalities, either therapeutically or with measures to prevent their further development, are agreed upon in the medical community. The value of testing for such abnormalities is indeed open to question when subjected to a cost-benefit analysis.

### *The Future of Multiphasic Testing*

While the success or failure of multiphasic testing is dependent on many variables, it can indeed serve as an effective and economical means of providing health screening examinations for large numbers of people. Multiphasic programs appear to hold considerable potential for populations with little or no current access to the medical care system. The potential is probably more limited with respect to the health care of well-educated, high socio-economic

groups for whom quality care is already available and who possess the sophistication to utilize it.

At least five factors will undoubtedly have a marked effect on the further expansion of multiphasic testing programs in the U.S. health care system. They are the following:

1. A general belief by the medical profession that testing can serve as an adjunct to their practices without endangering their patient relationships or their professional prerogatives. Disappointing numbers of patient referrals to multiphasic testing programs suggest that private physicians actually use available programs to a far more limited extent than many program directors had planned for, based on inquiries within the profession.

2. Based on needs within an area, a rational growth pattern with respect to the development of new programs so as to prevent unnecessary duplication and thus assure optimum utilization and minimum costs to patients being served.

3. The establishment of meaningful criteria for the evaluation of abnormalities in test findings in order for results to be of maximum benefit as diagnostic aids while the numbers of false positives and false negatives are minimized.

4. Further evaluation of testing program content, with emphasis on limiting tests to those which can be cost justified and to further design of programs meeting specific needs of various subgroups within the population.

5. The extent of coverage for multiphasic testing and effective follow-up care in programs of health insurance.

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# Medical Discipline and Personal Rights

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MEDICAL DISCIPLINE in California encompasses two major areas. One can be described as voluntary society discipline that may result in some impairment of practice rights but does not subject the offender to loss of legal right to practice medicine. This category includes medical society discipline, in-hospital medical staff discipline, and discipline by specialty societies.

The other category involves governmental restriction or loss of license and in California such penalties are the sole prerogative of the State Board of Medical Examiners.

Both categories of discipline are now accepted as involving rights—call them property or liberty, or quasi-property or liberty—that are entitled to the protection of the constitutional guarantee of due process of law. This little phrase “due process” is at the root of much of the frustration but it is a fact of life, growing every day.

The due process clause of our federal and state constitutions is one of the chief foundations on which personal rights have been built. While the concepts of due process and of personal rights have been with us at least since Patrick Henry, development and enlargement of the concepts in the past two decades have wrought drastic changes in the daily lives of all of us.

When the United States Supreme Court decided after 100 years to the contrary that “separate but equal” did not constitute due process, this country embarked on an expansion of indi-

vidual permission and protection of the person that has grown to immense proportions and shows no sign of slow-up or reversal.

Medical discipline has been greatly affected by the new emphasis on protection of the person. Decades ago, it was established that expulsion from a medical society could be lawfully accomplished only by adhering to procedural due process. Essentially this means that an accused member is entitled to know the charges against him, including what lawfully established rule he has violated, and he is entitled to adequate notice, a fair hearing and an opportunity to defend himself. He cannot be presumed guilty—his accusers must carry the burden of proof.

At first this concept was limited to medical society expulsion. It has now been expanded in some cases to hospital staff membership, and even to specialty society membership.

Within the past two years the personal right of an individual to due process has been extended to cover admission to membership, and in one case to admission to membership to a specialty society. That is, one cannot be excluded save by due process. Thus, all facets of discipline on the part of voluntary organizations have now been blanketed into the rigid requirements of due process of law. The courts have reasoned that while membership or lack of it may not totally deprive one of livelihood or property or liberty, nevertheless membership or lack of it does have a sufficient bearing on the individual's daily life to warrant legal protection by way of due process.

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Taken from a speech given before the monthly membership meeting of the Santa Clara County Medical Society, September 28, 1970.

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In one recent case, certification by a specialty society of allied health personnel was subjected to due process requirements, even though lack of certification had no economical consequences.

In the light of present day constitutional law, there is no doubt that medical discipline by medical societies must conform to the requirements of due process of law, no matter what the nature of the discipline imposed.

Since the protection of due process is a constitutional guarantee, laws passed by the Legislature cannot change the requirement.

Quite obviously, if professional society discipline is protected by due process, the more severe punishment meted out by licensing boards is bound to receive the same protection, and it does.

Before proceeding with the disciplinary powers and limitations of the Board of Medical Examiners, I should outline a new type of governmental discipline that came into being with the advent of Medi-Cal. Before California's implementation of Title XIX of the Social Security Act in 1966, physicians who received payment for services rendered from governmental agencies were subject to criminal punishment if they obtained money under false pretenses, or could be made to obtain "prior authorization" if medical review determined that they were perhaps overutilizing or providing substandard care.

However, discipline in the sense of prohibiting further participation in a governmental program was unknown. Actually, in the welfare field at least, the pre-1966 public assistance medical programs were quite limited and the disciplinary problem was not great.

With the advent of Medi-Cal, its total benefit structure and its huge public coverage—between one and a half and two million people—surveillance of practice patterns became much more important, and the term *peer review* soon became current in medicine.

The original Medi-Cal law was silent on the subject of discipline of physicians or other providers.

This legal vacuum resulted in frustration on the part of hard working committees that reviewed Medi-Cal alleged "abuse" cases.

In 1969 the Legislature enacted Section 14123 of the Welfare and Institutions Code. This section permits the Director of Health Care Services

to suspend any provider of services found guilty of wrongdoing, after charges, notice and hearing—that is, after procedural due process has taken place.

Temporary suspension before hearing is provided but it seems likely that the courts will hold such action unconstitutional as a violative of personal rights.

In any event, a few years from now, after quite a struggle, I think there will be a peer review system under Medi-Cal that will protect the constitutional guarantees of due process and at the same time permit implementation of the proper findings of medical review committees.

Up to this point, my references to due process have stressed the bearing that the due process concept has on organizations and groups seeking to impose discipline. There is another side of the coin that we must all realize, and that is that due process does protect personal rights against real abuse. For example, in legislative hearings on Medi-Cal and in legislative hearings on malpractice, it became quite apparent that some legislators equated a malpractice judgment or settlement with incompetence.

The reasoning was simplistic—namely, that payment of damages, either by way of judgment or settlement, means the physician was negligent. If he was negligent once, he must be negligent all the time; therefore, he is incompetent.

It was seriously proposed that license revocation should be permitted based solely on a malpractice judgment or settlement. If the Legislature ever does equate a settlement or judgment with incompetence, the due process clause will be the only recourse to avoid total injustice.

Every time the Board of Medical Examiners of the State of California suspends, restricts, or revokes a license, it must be prepared to defend itself in court and to establish that the accused physician received every right afforded him under the constitutional guarantee of due process. The court must be convinced that the Board gave adequate notice; that the charges against the accused were specific and identified the violation of law; that the accused had adequate notice, a fair hearing and adequate opportunity to defend himself.

Further, since license impairment proceedings are not unlike trials on criminal charges, the evidence adduced before the Board must have been



lawfully obtained within the current rules protecting accused persons against entrapment, search, seizure, wire-tapping, and the like.

Parenthetically, courts have permitted voluntary associations, such as medical societies, more latitude in the acquisition and production of evidence than is permitted by the Board of Medical Examiners.

I will now undertake to outline the medical disciplinary system in which the Board of Medical Examiners lives and to identify in general the scope of its activities.

While I do so, please remember the personal rights guaranteed to all accused persons which the Board must not violate.

The grounds upon which the Board may discipline a licensed physician are numerous and varied. I have heard it said that the only grounds upon which the Board may revoke a license are narcotics addiction and acute alcoholism. True, these are grounds, but they are not by far the only ones. There are many others, including conviction of a crime, aiding unlawful practice, prescribing dangerous drugs (for example, "goof balls") without previous examination of the patient or "medical indication therefore," willful betrayal of a professional secret, and deceptive advertising.

However, the most important causes for discipline are enumerated in Section 2361 of the California Business and Professions Code. These are: gross negligence, gross incompetence, gross immorality or the commission of any act involving moral turpitude, dishonesty or corruption.

An incompetent physician is a violator of the Medical Practice Act and can be disciplined by way of license revocation, suspension or restriction. The problem is proof. The Board cannot act unless there has been submitted to it legally acceptable evidence, procured without violating any personal rights, that establishes the existence of either gross negligence or gross incompetence.

The gathering of evidence and evaluation of whether it will "stand up in court" are of necessity and by virtue of constitutional law basic responsibilities of the Board and its supporting staff.

How does the Board carry out its disciplinary role? By and large, disciplinary inquiry is instigated by complaints submitted to the Board. Complaints originate from law enforcement

agencies, medical societies, individual members of the public, and institutions such as hospitals or pharmacies.

When a complaint is received, it must be referred by the Board to another governmental agency, the Division of Investigation of the Department of Professional and Vocational Standards. The Board of Medical Examiners is not independent or autonomous. It is an agency within the Department of Consumer Affairs, and its administrative function, as well as its financing, are in effect controlled by the department of which it is a unit.

Returning to the disciplinary process, after the Division of Investigation has conducted its field inquiry, the results obtained are forwarded to the Board's attorney, who by law is the Attorney General of the state. On receipt of the results of investigation, deputies in the Attorney General's office evaluate the file to determine whether there is "legal evidence" of a violation. If this test is passed, the complaint then goes to the staff of the Board of Medical Examiners and a formal written charge is prepared and signed by the executive secretary of the Board.

At that point, a "case" has begun. Under the California Administrative Procedure Act, which was adopted to provide due process before administrative agencies, the next step is that the written charge must be served on the accused physician, and he must be given adequate notice of time and place of hearing. In due course, a hearing is held either before the full Board or a District Review Committee, usually presided over by a hearing officer provided by the Division of Administrative Procedures. Following the formal hearing, a decision is made and if the accused is found guilty of the charges presented, disciplinary measures are invoked.

Then the accused physician may appeal to the courts. He may challenge the action of the Board on any of many grounds, including any failure to protect his rights, and any defect in any of the procedural steps from the time of the original complaint filed with the Board until the time of final decision. He may also challenge the weight of evidence before the Board.

Court review starts at the level of the Superior Court and may proceed through it to the Court of Appeal, and from the Court of Appeal to the State Supreme Court.

Assuming that a physician accused of violat-

ing the Medical Practice Act pursues all of his remedies to the very end, the time lag from the original complaint to the final decision can be years.

The ability of the Board to function within the framework of the protective legal system I have outlined depends in part on funds available to it and in part on the manpower assigned by the various agencies involved.

Recently I inquired of the executive secretary of the Board of Medical Examiners as to funds budgeted for investigation and disciplinary prosecution and as to personnel made available. I received a most interesting response:

"The amount of funds budgeted in the 1970-71 fiscal year which covers the period from July 1, 1970 to June 30, 1971 for services of the Division of Investigation is \$252,526. The amount allocated for legal advertising hearings and evidence is \$27,919. The amount for hearing services of the Office of Administrative Procedure is \$50,000, and the amount for Attorney General services is \$86,000, making a total of \$416,445.

"We believe the amount budgeted for the Office of Administrative Procedure and the Attorney General's Office is low due to the fact that the actual amount expended for the 1969-1970 fiscal year was \$101,281 for the Attorney General Services and \$60,453 for the Office of Administrative Procedure. The total budget allotment for the 1970-71 fiscal year is \$1,022,772.

"You will note that the expenditures do not include the services of the staff of the Board that are involved in connection with investigations and hearings.

"We have been advised by Mr. Ross, Chief of the Division of Investigation, that 41 investigators of that Division do work on complaints referred to them by the Board of Medical Examiners. However, *none of them spend full time on the activities of the Board.* [Italics supplied.]

"The number of deputies in the Attorney General's office who have handled requests for accusations from the Board are 2 in the Sacramento office, 2 in the San Francisco office and 3 in the Los Angeles office. Information received from the Attorney General's office indicates that the total number of hours spent by the deputies on work from the Board was 5,787.50. This would average out to approximately 3.21 full-time deputies on the basis of 1800 hours being a full year's work.

"The estimated accumulative surplus or amount available for appropriation as of June 30, 1971 will be \$2,833,423. None of this money can be expended by the Board unless authorized in the budget by the legislature or on the basis of deficiency allotment on a very definite showing of need for additional funds. I might say that we have been unable to secure additional funds by way of deficiency allotment funds."

I also asked for a breakdown of the number of charges or accusations heard by the Board under the gross negligence and gross incompetence clauses of Section 2361 of the Business and Professions Code. In response, I was informed a total of eight formal accusations have been filed charging violations of either the gross negligence or gross incompetence clauses, and that six of these eight cases have been completed.

Section 2361 has been in existence since 1965. You may well wonder why only eight accusations have been filed, alleging gross negligence or gross incompetence in the ensuing five years. I am sure the answer is found in the lengthy and involved procedural processes that must be gone through to comply with the constitutional personal rights guarantees.

Each step along the way must be carried out without error; otherwise, the entire case is likely to be "thrown out" when it reaches the courts. I have personally reviewed several of the accusations of gross incompetence or gross negligence that have been heard by the Board in the past several years and it is quite apparent that in each case the process of gathering legally competent evidence and then presenting that evidence to the Board was time-consuming and required many man-hours.

The Board cannot change the due process clause of the federal and state constitutions. The members of the Board and supporting staff are painfully aware that any failure at any stage of the proceeding to comply with due process will result in a court reversal of whatever disciplinary action may be taken.

Short of repeal of the Fourteenth Amendment to the Constitution of the United States, there are no shortcuts that can be achieved by legislative changes.

The question then is, What can be done? The Board of Medical Examiners is self-supporting—that is to say, its operating costs are met by the license renewal fees paid by physicians. The



physicians who are paying the bill have every reason to insist that, within available funds derived from fees, money will be budgeted to enable disciplinary functions to be carried out.

Physicians through their medical organizations need to become more deeply involved in the Board of Medical Examiners budgeting problems and to assist the Board to secure adequate financing. The state budget process is intricate and it starts long before the budget year. Right now the 1971-72 budget is well along its administrative development route. It is during the administrative development process that medicine should assist the Board.

On another front, consideration should be given to seeking legislation that would return to the Board its own investigators. You will recall that the letter from the executive secretary, which I quoted, mentioned the Division of Investigation and that 41 investigators worked part-time on complaints from the Board of Medical Examiners. The Division of Investigation is independent of the Board. Formerly, the Board had its own investigators working full-time for the Board and under Board supervision.

In one of the numerous reorganizational juggling acts that are supposed to increase governmental efficiency, the Board lost its investigators.

In my opinion, the Board at that time had a very competent staff, one which understood medical investigation and medicine's problems. I think legislation should be sought to return to the Board its own investigating group.

Consideration should be given to dividing the licensing and disciplining functions now the responsibility of a single board—the Board of Medical Examiners.

In the State of Washington some years ago, the disciplinary functions were taken away from the Washington Board of Medical Examiners and placed in a newly created board called the Disciplinary Board. I have received conflicting re-

ports as to the effectiveness of this separation of licensing and discipline. However, many Washington physicians are convinced that the existence of an entirely separate medical disciplinary board has increased the effectiveness of medical discipline. Whether it has accomplished as much as its supporters claim, I do not know.

Nevertheless, its popularity with Washington physicians warrants a first-hand inquiry into this approach to the problem.

One of the provisions in the Washington law that appeals to physicians is that they elect the members of the Disciplinary Board by their own vote. Members are not appointed by the governor, as is the case with medical boards in all other states.

Finally, I recommend that physicians who become members of professional relations committees or ethics committees, or other similar disciplinary committees, be given indoctrination courses covering medical ethics, the applicable by-laws of their societies and the state and national organizations, and the law of the land that is applicable to their functions.

This could be done in any one of several ways. Either locally through indoctrination courses given by each local society, or by the state association through periodic, statewide seminars or conferences.

Physicians are exposed to many types of conferences, ranging from postgraduate education to matters of malpractice, and I shudder at the thought of one more intrusion into one's limited leisure time. However, if committee members have a working understanding of the rules that govern, frustrating errors and mistakes will be minimized.

From what I have said, it may be seen that in my opinion new legislation won't achieve anything, but that understanding the law will have a beneficial influence on the efficacy and fairness of medical discipline.

# SAMA Summer Preceptorship Program

BARBARA GOTS, *Los Angeles*, AND MITSUO TOMITA, *San Francisco*

THIS SUMMER THE Student American Medical Association is establishing a summer preceptorship for medical students, placing them in community hospitals and clinics. The project is entitled MECO (Medical Education and Community Orientation); and the California Medical Association and the California Hospital Association have endorsed MECO and are participating in its development for summer, 1971.

The initial project was begun in Illinois in 1969, and has since expanded to 20 states. An in-depth study of the medical students, hospitals and physicians participating revealed that the program was generally a rewarding educational experience for those involved.

MECO is designed to permit the student to rotate through the clinical and non-clinical areas of a community hospital and the community it serves, under the direct supervision of physicians and staff. Under the direction of a community physician, the student will be able to observe and assist in the care of in-patients on the medical and surgical services and in the care of outpatients in the physician's office and extended care facilities. He will be able to study health and health care delivery problems specific

to that community and to formulate solutions to them.

It is hoped that by introducing the student to non-university, community hospitals and thus to future practice opportunities, he can better plan his medical education so that following his medical training, he may return to these areas to practice. MECO, therefore, provides the opportunity for community hospitals and practicing physicians to participate in undergraduate medical education, while simultaneously contributing to the alleviation of our current health care delivery crisis.

The practicing physician's knowledge of the community in which he practices will add immeasurably to the student's ability to observe, assess and participate in patient care. By working together, practicing physicians and medical students will discover a greater awareness of each other's attitudes and problems and those of the community.

Each student in the project is paid \$65 to \$80 a week educational stipend, plus room and board where available. The money for this is provided by the participating hospital.

Doctors interested in participating should contact their hospital's chief of staff or chief administrator, both of whom have already been contacted.

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The authors are SAMA-MECO State Project Coordinators. Mrs. Gots is a student at USC School of Medicine and Mr. Tomita, a student at UC, San Francisco, School of Medicine.



# Hemodynamic Effects of Cardiac Arrhythmias

ALAN G. BARTEL, M.D., AND  
HENRY D. MCINTOSH, M.D.

*Material Supplied by the American Heart Association*

Recent advances in intensive cardiac care and widespread use of continuous electrocardiographic monitoring have emphasized the frequency and nature of cardiac rhythm disturbances. Recognition, however, requires at least a based on an understanding of the "natural history" and hemodynamic consequence of a specific arrhythmia.

The net effect of a particular arrhythmia is determined by the circulatory state of the patient as well as the nature of the rhythm disturbance. Usually "benign" rhythm disturbances such as bigeminy and atrial fibrillation, occurring in a patient with limited cardiac reserve, may rapidly result in severe cardiac decompensation with myocardial ischemia, hypoxia, and hypotension, shock, or death. Furthermore, the arrhythmia may compromise the blood supply to the end organs and thus produce myocardial infarction, renal failure, cerebrovascular accidents, hepatic necrosis, infarction of the intestinal tract and the like.

Since many arrhythmias are transient and cause only minor alterations of the circulation, or occur in patients with less severely compromised circulation, the symptoms produced may be

vague and nonspecific. Such symptoms include palpitations, episodes of weakness and fatigue. On the other hand, they may cause more serious symptoms and signs such as transient neurological deficits, lapses of memory, presyncope or syncope, increasing congestive heart failure, increasing angina, and intermittent claudication.

It must be borne in mind that the hemodynamic effects resulting from an arrhythmia are not due solely to the changes of cardiac function. The observed response of the circulation may well be due to peripheral effects. Thus, the status of the peripheral resistance, blood volume, baroreceptor activity, and venous return must be considered in any critical analysis of arrhythmic effects.

Rather than discussing the hemodynamics of particular arrhythmias, it is useful to consider the physiologic alterations that may be produced by any arrhythmia.

## Rate

The rate of contraction of the ventricles will determine the cardiac output if the volume of blood ejected with each stroke remains unchanged. Rapid or slow rates critically affect hemodynamics. Bradycardia may produce profound effects, especially when the stroke volume cannot increase and peripheral compensatory mechanisms are inadequate. In many patients, however, the heart may compensate physiologically during slow heart rates by increasing stroke volume due to increased ventricular filling and ventricular wall pressure (Starling's law). The net effect of increased stroke volume may compensate for a decreased heart rate resulting in insignificant changes in cardiac output which can be adequately compensated for by an increase in peripheral resistance.

In addition, bradyarrhythmias may permit the discharge of "irritable" pacemaker foci, thus predisposing to tachyarrhythmias and producing bradycardia-tachycardia syndromes.

If the heart rate increases beyond a critical rate (varying with the basic status of the cardiovascular system) the ventricle fills incompletely during diastole, resulting in a decreased output per beat. A similar, but transient, effect occurs during rapid irregular rhythms or multiple premature contractions (the earlier the contraction, the smaller the subsequent output).

Instructor in Medicine (Bartel); Professor of Medicine and Chief, Cardiovascular Division, Cardiovascular Laboratory, Department of Medicine (McIntosh), Duke University Medical Center, Durham, N.C.

## "Atrial Kick"

The importance of coordinated contractions of the atria and ventricles and the contribution of atrial systole to ventricular filling (appreciated by Harvey in 1628), have recently been reemphasized. In normal hearts, atrial contraction may add between 10 and 20 percent of ventricular volume, whereas in severe valvular heart disease, such as mitral stenosis, the diastolic ventricular volume may increase by more than 50 percent during the period of atrial systole. It has been demonstrated that with an effective well placed atrial contraction a higher ventricular end-diastolic volume may be obtained with a lower mean atrial pressure than occurs when the atria are not functioning properly. Insufficiency of the AV valves may also be produced by the loss of coordinated atrial and ventricular contractions, resulting in detrimental cardiovascular effects.

The hemodynamic effects of a rapid or slow heart beat may be minimal if the "atrial kick" is preserved, but when it is lost, the additional insult may cause decompensation.

Common examples of tachycardia associated with loss of coordinated atrial and ventricular contractions are atrial fibrillation, junctional (nodal) rhythm, and partial (second degree) heart block. The commonly used types of ventricular pacemakers should also be included, since atrial and ventricular contraction are not synchronized.

## Method of Ventricular Activation

Several studies have shown that alteration of the normal sequence of activation of ventricular contraction results in adverse hemodynamic effects. Given two arrhythmias with identical coordination of atrial and ventricular contraction and the same heart rate, one demonstrating an abnormal sequence of ventricular activation (that is, aberrant conduction) and the other normal sequence of activation, the former will result in greater alteration of hemodynamics. Such alterations, in addition to the absence of an effective atrial kick, explain why ventricular tachycardia or junctional tachycardia with aberrant conduction is less well tolerated than atrial tachycardia. It may also explain why patients with sinus bradycardia may deteriorate rather

than improve when the heart rate is increased by fixed rate ventricular pacing (loss of atrial kick and normal ventricular activation).

## Effects of Pharmacologic Agents

It should be mentioned that in the conversion of arrhythmias, especially tachycardias, to a normal sinus mechanism by the use of drugs, the frequent myocardial depressant effect of the drugs may result in a significant, although usually transient, fall in cardiac output. Hence the administration of drugs such as lidocaine, quinidine, procainamide (Pronestyl®), diphenylhydantoin sodium (Dilantin®), and propranolol hydrochloride for management of arrhythmias should be carried out under careful monitoring; the smallest effective dose should be used with the expectation that the patient may experience a temporary decrease in cardiac output even after normal rhythm has been established.

## Conclusion

The clinical manifestations of cardiac arrhythmias may produce unusual or ill-defined symptom complexes. The occurrence of incipient or increasing congestive heart failure, angina pectoris, intermittent claudication or episodic dizziness, fatigue, transient neurological disturbances or paroxysms of dyspnea should alert the physician to consider the possibility of a cardiac arrhythmia.

It can be concluded that the hemodynamic effects of arrhythmias depend upon the underlying status of the myocardium, blood vessels, and end organs, the heart rate, preservation of the "atrial kick," and normal sequence of activation of the ventricles. The altered hemodynamic effects may be further aggravated by the effects of pharmacologic agents used to correct the arrhythmia.



# Physicians' Employees Must Not Orally Transmit Narcotic Prescriptions

A. M. GILDER, PHARM.D., *Pomona*

IT HAS BEEN REPORTED that physicians' employees have been attempting to orally transmit prescription orders for narcotic drugs.

The Business and Professions Code, Section 4036.2 states:

## *Persons Authorized To Transcribe Oral Prescriptions:*

"Notwithstanding any other provision of law, a prescriber may authorize his employee to orally

The author is an executive member, Legislative Committee, California Employee Pharmacist Association.

transmit a prescription to the furnisher, if the prescriber gives the furnisher within a reasonable time written evidence of the employee's authorization. The furnisher shall record the name of the employee of the prescriber who transmits the order.

(NOTE): *This section shall not apply to orders for narcotics as defined in Division 10 of the Health and Safety Code."*

The Code's interpretation is as follows:

a. Any unauthorized person who utters a new narcotic prescription by telephone communication can be charged with practicing medicine without a license.

b. A physician who directs an unauthorized person to practice medicine by issuing original narcotic prescription orders is jeopardizing his license.

The above communication is intended as a reminder that adherence to legal requirements is in the best interest of public health.

## CLINCHING THE DIAGNOSIS OF CELIAC DISEASE

Do you think a small bowel biopsy is necessary in each child with documented malabsorption in whom a gluten sensitivity is suspected, or are you willing to rely on the clinical response to gluten withdrawal?

"I think if a child has documented malabsorption and an abnormal d-xylose test, I'd like to do a biopsy if I possibly could because, in my mind, I'm committing that child to a gluten-free diet until after adolescence.

"I try to insist that a child with proven celiac disease remain on a gluten-free diet until he's finished his growing. When he reaches adulthood, I let him choose. Some people become much less sensitive to gluten so that they can eat a little if they want. They usually sort of titer themselves. They keep the weight they want and the symptoms they want. If they want to be completely asymptomatic, then they follow the diet strictly.

"So I would try to get a biopsy in anyone with proven malabsorption, proven steatorrhea, and proven low xylose. I definitely think that you should get a biopsy if you possibly can. It's important because with it you make the specific diagnosis and you can say that 95 percent of the time the patient will respond to a gluten-free diet. You can tell yourself and the parents and it reassures everybody."

—THEODORE M. BAYLESS, M.D., Baltimore  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## The Control of Rubella In California

LIVE RUBELLA VIRUS VACCINE was first licensed for use in the United States in June 1969 and has been in extensive use in California for approximately one year. As of March 1971, more than one million children in California have received the vaccine, and 35 of California's 58 local health jurisdictions have conducted intensive rubella immunization activities.

To date, the use of the vaccine nationally has been somewhat more intensive than in California. Four states have immunized 80 percent or more of their one- through eleven-year-old populations, and 28 million doses of the vaccine have been distributed throughout the United States.<sup>1</sup> This backlog of experience permits some review of the recommendations for use of the vaccine and some comments on the questions about the vaccine that are most frequently asked.

### The Approach to Vaccine Use

Three approaches are advocated for the effective control of rubella through immunization. They are: 1) immunization of all children from age one through eleven years, 2) immunization of adolescent girls, age 11 through 13 years, 3) immunization of rubella-susceptible women in the childbearing ages. A brief discussion of each approach is necessary to view in proper perspective the current Rubella Control Program in California. The recommendations jointly agreed upon by the California Medical Association and the State Department of Public Health in consultation with local health officers provide a framework in which each of these approaches may be pursued concurrently.<sup>2</sup>

1. Since children constitute the major source for spread of rubella infection to susceptible pregnant women, effective control of the rubella problem can be achieved by eliminating or significantly reducing the transmission of virus in the pediatric population. The vaccine has been shown to be safe and protective for children. Programs in other areas of the United States have shown that 80 to 90 percent of children can be immunized in community sponsored campaigns in a relatively short period. At present, this approach is the only feasible method to achieve the rapid immunization of a sufficient proportion of the population for effective control of the rubella problem within the next year or two. Furthermore children are easily reached by immunization programs. Principally for these two reasons public programs have placed primary emphasis on this approach.

2. The immunization of all girls aged 11 through 13 years, that is, the group just before the childbearing ages, can reduce the incidence of congenital rubella syndrome infants when these girls reach their childbearing period, about five to ten years from now. However, this approach can have virtually no immediate impact and would not prevent the anticipated epidemic of rubella which is forecast for the early 1970's.

3. Within the framework of the joint recommendations for rubella vaccine use, developed by the California Medical Association and the State Health Department, the immunization of women in the childbearing age group is recommended. It is not known whether the vaccine virus itself may cause fetal damage, but this risk must be assumed if given to a rubella-susceptible woman during pregnancy. Women should be considered for immunization on an individual basis and only if appropriate measures are taken to avoid administration of vaccine shortly before or during pregnancy. The necessity of avoiding inadvertent immunization of women shortly before or during pregnancy precludes the development of public programs which could reach large numbers of women in a short period.<sup>3</sup> Considerable time and



effort would be needed to achieve significant reductions in the incidence of congenital rubella syndrome infants if this were the only approach used.

## Comments on Questions About the Vaccine

*Vaccine Reactions.* Experience since licensure has indicated that transient joint pain and related complaints such as numbness and paresthesia in an extremity are the most troublesome of the vaccine-associated reactions.<sup>4</sup> The national experience in this regard is consistent with that in California. Continuing experience has confirmed that the frequency of such complaints is higher in women over the age of 25 years than in children, and is higher in those receiving the vaccine strain produced in dog kidney cell culture than with the strains grown in duck embryo or rabbit kidney cell culture.

*Virus "Shedding" and Communicability.* The consistent appearance of rubella vaccine virus in the pharynx of susceptible vaccinees can be demonstrated by the use of sensitive isolation techniques. This has raised the question that some hazard of transmission of the virus to susceptible pregnant women might exist. Both before and after licensing, studies have been conducted to explore the possibility of rubella vaccine virus transmission under a variety of circumstances—for example, institutionalized child to child, institutionalized adult to adult, household sibling to sibling, child to mother, mother to infant, and classmate to classmate in schools.<sup>5</sup> The most recent study of this type, reported by Scott and Byrne,<sup>6</sup> involved 121 rubella-susceptible pregnant women who were carefully followed by serological testing during and after a state-wide rubella immunization campaign in Rhode Island. This study confirmed the findings of earlier studies that immunization of children presents no hazard to pregnant women.

After reviewing the data on transmissibility of rubella vaccine virus at its most recent meeting in October, 1970, the Committee on Infectious Diseases of the American Academy of Pediatrics issued the following statement: "The Committee was reassured by two recent studies including approximately 200 rubella susceptible pregnant women who remained seronegative in the face of widespread community vaccination; in some instances such women were exposed to vaccine re-

cipients in family, school and other situations of close contact."

*Reinfection of Vaccinees.* It is known that in virus infections which have been extensively studied, such as poliomyelitis and rubeola, immune persons when re-exposed may develop clinically inapparent reinfections. This phenomenon has also been noted with rubella. The reinfections tend to be subclinical, highly abbreviated from a virological point of view, and most common in persons with relatively low antibody levels.<sup>4</sup>

The Committee on Infectious Diseases of the American Academy of Pediatrics also spoke to this question in the following statement: "Although reinfection on exposure to natural rubella has been found to occur more frequently among vaccinees than in naturally immune persons, transmission of virus to susceptible contacts has not been demonstrated. Since these episodes of reinfection have not been accompanied by detectable viremia, it is unlikely that the fetus of a vaccine-immune woman would be infected."<sup>7</sup>

## Conclusion

An effective vaccine is available to control rubella but it will require the cooperative efforts of all private and public medical groups to achieve significant results without undue delay. The immediate priority of all physicians and public health workers is to prevent the disastrous consequences of another rubella epidemic which is expected within the next few years. No one at this time can give any absolute assurance that the immunization of children will be completely successful or will be the primary method for the future, but no other alternative currently available would be effective in a short time. Continued surveillance of the rubella problem is essential and as more experience is accumulated the present public programs can be modified if necessary.

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5. Krugman, S (Ed): Proceedings of the International Conference on Rubella Immunization, Bethesda, Md. Feb. 18-20, 1969. *Amer J Dis Child* 118:3-410, 1969
6. Scott HD, Byrne EB: Exposure of susceptible pregnant women to rubella vaccinees. *JAMA* 215:609-612, 1971
7. Committee Statement, Committee on Infectious Disease, American Academy of Pediatrics, Dec. 1, 1970

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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

CARPENTER, STEWART, JR., Newport Beach. Died January 6, 1971 at Balboa Island of carcinoma, aged 45. Graduate of University of Texas School of Medicine, Galveston, 1950. Licensed in California in 1951. Doctor Carpenter was a member of the Orange County Medical Association.

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CLEMMER, HUGH, Lancaster. Died January 30, 1971 in Lancaster, aged 46. Graduate of University of Pittsburgh School of Medicine, 1948. Licensed in California in 1951. Doctor Clemmer was a member of the Los Angeles County Medical Association.

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CRANE, JACKSON TEMPLE, Chico. Died January 27, 1971 near Pulga, aged 48. Graduate of University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1946. Doctor Crane was a member of the Butte-Glenn Medical Society.

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DANIEL, WILLIAM HARDY, Vista. Died February 4, 1971 in Oceanside of cerebrovascular accident, aged 81. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1915. Licensed in California in 1915. Doctor Daniel was a member of the Los Angeles County Medical Association.

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DEVLIN, PATRICK JOSEPH, Long Beach. Died February 12, 1971 in Los Alamitos of ventricular fibrillation, aged 50. Graduate of Queen's University Faculty of Medicine, Belfast, Ireland, 1950. Licensed in California in 1956. Doctor Devlin was a member of the Los Angeles County Medical Association.

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ESBERG, HANS, San Francisco. Died January 29, 1971 in San Francisco, aged 78. Graduate of Thuringische Landesuniversität Medizinische Fakultät, Jena, Thuringia, Germany, 1921. Licensed in California in 1940. Doctor

Esberg was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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FINDLAY, HENRY VERRILL, Santa Barbara. Died February 17, 1971 in Santa Barbara, aged 68. Graduate of Harvard Medical School, Boston, 1928. Licensed in California in 1933. Doctor Findlay was a member of the Santa Barbara County Medical Society.

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FISHBURN, GEORGE WASHINGTON, San Diego. Died February 10, 1971 in San Diego, aged 56. Graduate of Medical College of Virginia, Richmond, 1943. Licensed in California in 1950. Doctor Fishburn was a member of the San Diego County Medical Society.

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GREENBAUM, GEORGE BENJAMIN, Los Angeles. Died January 20, 1971 in Los Angeles of arteriosclerotic heart disease, aged 87. Graduate of Northwestern University Medical School, Chicago, 1909. Licensed in California in 1924. Doctor Greenbaum was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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HOPKINS, MAURICE A., Sacramento. Died January 12, 1971 in Sacramento, aged 71. Graduate of Jefferson Medical College of Philadelphia, 1926. Licensed in California in 1928. Doctor Hopkins was a member of the Sacramento County Medical Society.

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KANDBINDER, ALFRED F., Monterey. Died December 30, 1970 in Monterey of ventricular fibrillation, aged 52. Graduate of University of Illinois College of Medicine, Chicago, 1943. Licensed in California in 1947. Doctor Kandlbinder was a member of the Monterey County Medical Society.

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LARSON, VIRGIL C., Orinda. Died December 27, 1970 in Walnut Creek, aged 61. Graduate of University of Oregon Medical School, Portland, 1938. Licensed in California in 1955. Doctor Larson was a member of the Alameda-Contra Costa Medical Association.

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MARSH, NORMAN E., San Bernardino. Died February 16, 1971 in San Bernardino, aged 58. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1942. Doctor Marsh was a member of the San Bernardino County Medical Society.



PANCOAST, CHARLES EDWARD, Covina. Died January 31, 1971 in Covina of heart disease, aged 69. Graduate of University of Arkansas School of Medicine, Little Rock, 1938. Licensed in California in 1939. Doctor Pancoast was a member of the Los Angeles County Medical Association.

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POWIS, HERBERT S., Arbutle. Died January 21, 1971 in Colusa, aged 76. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1915. Licensed in California in 1915. M.D. degree from California College of Medicine, 1962. Doctor Powis was a member of the Yuba-Sutter-Colusa County Medical Society.

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ROTHSCHILD, PHILIP D., Encino. Died December 13, 1970 in Van Nuys, aged 36. Graduate of University of California School of Medicine, San Francisco, 1959. Licensed in California in 1960. Doctor Rothschild was a member of the Los Angeles County Medical Association.

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ROY, GUSTAVE A., Orange. Died January 26, 1971 in Costa Mesa, aged 61. Graduate of University of Kansas School of Medicine, Lawrence-Kansas City, 1932. Licensed in California in 1954. Doctor Roy was an associate member of the Orange County Medical Association.

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SAVAGE, JOSEPH CARR, Los Angeles. Died December 19, 1970 in Los Angeles of cancer, aged 80. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1927. Doctor Savage was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

SCOTT, MILDRED ESTHER, San Bernardino. Died February 13, 1971 in San Bernardino, aged 64. Graduate of University of Kansas School of Medicine, Lawrence-Kansas City, 1930. Licensed in California in 1959. Doctor Scott was a member of the San Bernardino County Medical Society.

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SMITH, SAMUEL WARREN, Oakland. Died February 10, 1971 in Berkeley of lymphosarcoma, aged 61. Graduate of University of California Medical School, Berkeley-San Francisco, 1942. Licensed in California in 1942. Doctor Smith was a member of the Alameda-Contra Costa Medical Association.

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TAYLOR, JO ANN TANNER, Glendale. Died February 1, 1971 in Orange of cancer, aged 50. Graduate of Harvard Medical School, Boston, 1949. Licensed in California in 1950. Doctor Taylor was a member of the Los Angeles County Medical Association.

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THAL, FRED JOSEPH, San Francisco. Died February 15, 1971 in San Francisco, aged 65. Graduate of Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, Prussia, 1930. Licensed in California in 1950. Doctor Thal was a member of the San Francisco Medical Society.

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WILHELM, LOUIS F. X., Los Angeles. Died January 27, 1971 in Los Angeles of coronary occlusion, aged 76. Graduate of St. Louis University School of Medicine, 1920. Licensed in California in 1926. Doctor Wilhelm was a member of the Los Angeles County Medical Association.

## DIAGNOSING MYASTHENIA GRAVIS

"When a patient comes in with a variable sort of facial weakness, especially ptosis or dysphagia or a nasal voice that is better in the morning and gets worse as the day goes on, he has myasthenia gravis until proven otherwise. This condition can be diagnosed properly by an edrophonium (Tensilon®) test which is dramatically rather than weakly positive. This can be performed in the office, but I always carry around a little atropine when I'm doing them because the vagal side-effects can be fairly dramatic in some patients. I also start off with only 0.2 cc of Tensilon—to see how it and the patient get along."

—JOHN H. GARDNER, M.D., Cleveland

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 15, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

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# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**MARIJUANA: THE NEW PROHIBITION**—John Kaplan, Professor of Law, Stanford University, Stanford, World Publishing Company, New York and Cleveland, 1970. 387 pages, \$8.50.

Here is a book by an attorney on a subject which the young of America and the American establishment consider of importance. And the difference in attitude towards marijuana on the part of the young and the establishment may in many communities be a most important feature of the generation gap.

Professor Kaplan was appointed in 1966 by the California Senate to a committee to revise the California Penal Code, last completely revised in 1872. By chance he was assigned the drug laws, about which he felt he had no knowledge or experience except that which he had acquired as a one-time prosecutor as Assistant United States Attorney. It became apparent at once that the key drug problem in California was the treatment of marijuana. Not until the treatment of marijuana was intelligently handled would progress in the broader area of drug abuse be possible.

*Marijuana: The New Prohibition* reviews the history of marijuana, how in 1937, four years after Prohibition ended, Congress outlawed the sale, possession, and use of marijuana. Professor Kaplan points out that the measure of the wisdom of any law is the measure of its total social and financial costs and the benefits that derive from this outlay. This book is an attempt to measure the costs of the criminalization of marijuana and concludes that the costs far outweigh the benefits.

The costs of the marijuana laws are not only financial, but involve removing the police from the pursuit of those involved in crimes against others, almost routine violation of civil liberties, and alienation both of youth and the police. There were about 50,000 arrests for marijuana use in California in 1968, and by Professor Kaplan's best estimates about one-third of California youth had used marijuana.

Dr. Kaplan then reviews in detail the evidence available against the use of and for the "criminalization" of marijuana, and finds it weak and flimsy.

Marijuana has become the symbol of a host of major conflicts in our society and though it is an oversimplification to say that marijuana users are long-haired hippies, many users do focus on immediate experience, are non-competitive, and not interested in acquisition of wealth. This involves a new life style which the establishment, including the police, finds threatening.

What are the ordinary effects of marijuana use? The everyday effects of marijuana—not the ones usually given for criminalization—are relaxation, euphoria, and a feeling that one's senses have been sharpened. This appears to be principally a focusing on the present, which can be a source of joy, or can be frightening.

The author then analyzes the evidence for and against the various accusations to which marijuana has been subjected—that it leads to aggression and to violence (the

opposite appears generally true), possible long-term effects, possible addictiveness, effect on driving capacity, and that its users progress to the use of more dangerous drugs. There is little evidence for this—for instance, in the Blum study on heroin, heroin users had used:—

Alcohol	100%	Sedatives	73%	Hallucinogens	50%
Tobacco	95%	Amphetamines	66%		
Marijuana	78%	Tranquillizers	62%		

and among marijuana users in a college population, heroin is virtually unknown—less than 1.5 percent.

Kaplan writes cogently and well, and the reader is carried along. The book is fascinating to the physician, and carries the special viewpoint of a scholarly attorney, a perspective most salutary to the conscientious physician who may see few limits to his responsibilities to society (and may get over his head in legal and social waters).

Kaplan ends *Marijuana: The New Prohibition* with an analysis of the possible alternatives open to American society in dealing with marijuana and draws conclusions with which we may not agree, but presented with a clarity which we are compelled to accept.

Required reading for all physicians relating to young people, schools, colleges, or interested in one of the major social problems of the day.

TALCOTT BATES, M.D.

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**PROGRESS IN GASTROENTEROLOGY**—Volume II—Edited by George B. Jerzy Glass, M.D., New York Medical College, New York, N.Y. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 543 pages, \$29.50.

This excellent book is the second volume of a series on selected new topics in Gastroenterology. The editor, Dr. George B. Jerzy Glass of New York Medical College has assembled 28 chapters by 53 authors, including many from Canada and Europe. This volume has good balance between basic science and clinical medicine. Basic science material is clearly presented about such current subjects as back diffusion of acid in gastric mucosa, antibodies to gastrin, and intestinal flora in health and disease. Clinical subjects of great interest include x-ray features of hiatal hernia, the Zollinger-Ellison syndrome and celiac disease.

Special chapters are written on Pediatric Gastroenterology and the role of the Intensive Care Unit in Clinical Gastroenterology. Two other well-written chapters of great value include those of primary and secondary disaccharidase deficiencies and toxic dilatation of the colon in ulcerative colitis.

This fine volume should be in the library of internists, gastroenterologists, general practitioners, surgeons, radiologists and pediatricians. It is up to date, well-written, and for the most part very helpful to all practitioners of clinical medicine.

DWIGHT L. WILBUR III, M.D.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(Formerly WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a Health Services and Mental Health Administration grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ALCOHOLISM AND DRUG USE

May 15-16—Drug Abuse. UCSF at Preston Hall, Presbyterian Church, Mendocino. Saturday-Sunday. Changing Patterns of Drug Abuse, Former Addicts, The Professional as a Member of a Self-Help Program, Methadone for Narcotics Addicts, Impact of Drug Abuse on Crime in Mendocino County, Nature of Lost War on Drug Abuse, Drug Use, Legalized Drug Abuse. \$25. 11 hrs.

May 20—Methods of Treating Drug Abuse: Approaches for the 70's. University of California Extension, Riverside at University Commons, Riverside. Thursday. Emergency and long-range treatment of drug users, methadone treatment, emergency medical treatment, community resources for treating drug abuse. Contact: Gwen Andracke, University of California Extension, Riverside 92502. (714) 787-4346.

June 28-July 2—Community Mental Health Approaches to the Problem of Drugs. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

July 12-16—Community Mental Health Approaches to the Problem of Alcoholism. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

## CANCER

May 17-19—Second National Conference on Breast Cancer. American Cancer Society at Century Plaza Hotel, Los Angeles. Monday-Wednesday. Newer Concepts

in Management, Incidence and Mortality, High Risk Groups, The Pill, Viruses, Immunology, Cell Kinetics, Genetics, Animal Experimentation, Early Breast Cancer, Detection and Screening, Management of Primary Operable Breast Cancer, Rehabilitation. Contact: Esther Kelley, Prof. Ed. Dept., ACS, 219 E. 42nd St., New York 10017. (212) 867-3700.

June 4-5—Cancer Conference. USC. Friday-Saturday.

Continuously—Tumor Board—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital,

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 455-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, School of Medicine, University of California, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



Torrance. Fridays 2-3 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## COMMUNITY MEDICINE

Continuously—Community Medicine Seminar. Department of Community Medicine, UCSD. September-June, second Friday monthly. Contact: UCSD.

## MEDICINE

May 15—Oral Lesions in Dermatology. STAN. Saturday.

May 16—Ventilation Perfusion Relationships. USC. Sunday.

May 16-19—National Tuberculosis and Respiratory Disease Association. Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: James E. Perkins, M.D., Managing Dir., NTARDA, 1740 Broadway, New York 10019. (212) 245-8000.

May 16-19—American Thoracic Society. Hilton and Biltmore Hotels, Los Angeles. Sunday-Wednesday. Contact: Robert Weymueller, ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 19-20—Coronary Artery Disease. USC at Rancho Los Amigos Hospital, Downey. Wednesday-Thursday.

May 20-22—Pulmonary Thromboembolism—1971. UCSD and American College of Chest Physicians at UCSD. Thursday-Sunday. Pathogenesis of venous thrombosis and pulmonary embolism, experimental models in thromboembolism, pathologic considerations in thromboembolism, cardiopulmonary pathophysiology in pulmonary embolism, diagnosis of venous thrombosis and pulmonary embolism, treatment, recent investigations. \$100 members, \$125 others. 18 hrs. Contact: UCSD.

May 21—Clinical Problems in Angina Pectoris. STAN at VA Hospital, Palo Alto. Friday. Common clinical problems, historical and physical signs, interpretation of electrocardiogram, use of phonocardiogram and treadmill exercise tests, hemodynamics, coronary arteriography, evaluation of left ventricular function, variant forms of angina, atypical clinical manifestations.

May 26—Los Angeles County Heart Association—Annual Meeting. Hilton Hotel, Los Angeles. Wednesday. Contact: LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

May 27-29—Advances in Endocrinology and Metabolism. UCSF. Thursday-Saturday.

June 1-4—Selected Topics on the Pathophysiology of Clinical Gastroenterology. UCSF and American College of Physicians at UCSF. Tuesday-Friday. Esophagus—structure, function and diseases including reflux; Stomach—evaluation of gastric secretion, diseases; Small intestine—small gut absorption and histology, diseases; Liver—evaluation of function and diseases; Colon—roentgenology and diseases; Pancreas—pancreatic secretion and diseases; Biliary tract—function of bile, gallstones. Esophagitis and stricture, peptic ulcer, malabsorption diseases, hepatic and cirrhosis, cholelithiasis, inflammatory diseases of the gut. Contact: UCSF.

June 5—Tuberculosis and Microbacteriology Today. UCSF. Saturday. Mycobacterial Diseases in Man, Tuberculosis Bacteriology Services Offered in California, Recommended Laboratory Methods, Drug Susceptibility Testing, Identification of Microbacteria Organisms Confused with Mycobacteria, Safety and Quality Control. 6 hrs.

June 14-July 2—Coronary Care for Physicians Training Program. CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three-week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

June 16-19—Third Annual Cerebral Function Symposium. Annual Cerebral Function Symposium at Hotel del Coronado, Coronado. Wednesday-Saturday. Hemispherectomy and Cerebral Function. Contact: W. Lynn Smith, Ph.D., Suite 1120, Franklin Medical Center, 2045 Franklin, Denver 80205. (303) 534-0903.

June 18-19—Selected Subjects in Electrocardiography. UCSF and Mt. Zion Hospital and Medical Center at Hilton Hotel, San Francisco. Friday-Saturday. Arrhythmias, conduction disturbances, other selected topics in electrocardiography.

June 22-23—American Diabetes Association. Sheraton-Palace Hotel, San Francisco. Tuesday-Wednesday. Contact: H. Richard Connelley, Exec. Dir., 18 E. 48th St., New York 10017. (212) 752-8550.

June 24-26—Endocrine Society. Hilton Hotel, San Francisco. Thursday-Saturday. Contact: Mrs. Nona Lee Mattox, Exec. Sec., ES, 1211 N. Shartel, Oklahoma City 73103. (405) 232-8747.

July 5-16—Coronary Care Unit Program for Physicians. CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

July 24—Pathogenesis and Management of Fluid and Electrolyte Imbalance. PMC. Saturday. Second in a series of four workshops. \$50.

August 18-22—Advanced Seminars in Internal Medicine. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday. 24 hrs.

August 30-September 2—Epidermal Wound Healing. UCSF at Del Monte Lodge, Pebble Beach. Monday-Thursday. Cellular Facets of Wound Repair, Cell Kinetics, Quantitation of Repair, Dermal-Epidermal Interactions, Physical and Chemical Factors Affecting Repair.

September 8-12—1971 Advanced Seminars in Dermatology. UCI at Newporter Inn, Newport Beach. Wednesday-Sunday. Microbiology of the Skin, Carcinogenesis and Cutaneous Cancer. \$100. 40 hrs. Contact: James Graham, M.D., Dept. of Medicine, UCI. (714) 633-9393, ext. 172.

September 13-October 1—Coronary Care for Physicians Training Program. See Medicine, June 14-July 2.

September 19—Fifteenth Annual Physicians Symposium on Cardiovascular Disease. Santa Barbara and Ventura Counties Heart Associations at Biltmore Hotel, Santa Barbara. Sunday. \$20. 7 hrs. Contact: Mrs. Sara Clyde, Exec. Dir., SBCHA, 18 La Arcadia Ct., Santa Barbara 93103. (805) 963-1541.

September 22—Eleventh Annual Medical Symposium on Kidney Disease. Kidney Foundation of Southern California at Ambassador Hotel, Los Angeles. Wednesday. \$25. 8 hrs. Contact: Leonard Gottlieb, Exec. Dir., KFSC, 5880 San Vicente Blvd., Los Angeles 90019. (213) 936-5229.

September 30-November 29—Current Concepts of Medical Oncology. UCLA. Thursdays weekly, except November 29.

Continuously—Training of Physicians in Modern Concepts of Pulmonary Care. CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, M.D., LLU.

Continuously—Coronary Care. St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—Neurological Sciences. St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—Continuing Education in Internal Medicine—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—Training for Physicians in Nephrology. CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—Training for Physicians in General Internal Medicine. CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—Training in the Procedure of Tonometry. Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California St., San Francisco 94118. (415) 387-0934.

Continuously—Medico-Surgical Cardiovascular Seminar. STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

Continuously—Cardiology Conferences—CRMP Area III. Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

#### Grand Rounds—Medicine

##### Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

##### Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

##### Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.



## Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## MENTAL RETARDATION

May 23-June 4—Mental Retardation Workshop. UCLA. Two weeks.

June 21-25—Implications for Future Planning in Mental Retardation: Research and Legislative Changes. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

## OBSTETRICS AND GYNECOLOGY

May 15—Gynecological Diseases. See Radiology-Pathology, May 15.

May 15—The Menopause and Its Treatment. UCSD. Saturday. Emotional and physical problems, gynecological changes—function and complications of estrogen therapy, bone problems and loss of height, skin problems, male menopause. \$10. 4½ hrs.

May 17-19—Second National Conference on Breast Cancer. See Cancer, May 17-19.

May 21-22—Sixteenth Annual Obstetrics and Gynecology Symposium. Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Coordinator, Education and Research, Room 6014, SCPMG, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

May 26-29—The High Risk Infant: Early Detection and Preventive Intervention. See Pediatrics, May 26-29.

June 4-6—Therapeutic Abortion. PMC. Friday-Sunday. Techniques, social and psychological aspects—counseling, prevention of recurrence, effects on patient and family, attitudes of personnel. \$90.

August 15-18—Fourth Annual Advanced Seminar in Obstetrics and Gynecology. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday. 24 hrs.

September 16-18—Obstetrics and Gynecology Program. UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

## Grand Rounds—Obstetrics and Gynecology

### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

11:30 a.m., First Floor Auditorium, Room 13-105, UCLA Medical Center. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU

### Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

### Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

### Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

## PEDIATRICS

May 15-16—Northern California Chapter, American Academy of Pediatrics—Annual Spring Meeting. Yosemite Lodge, Yosemite. Saturday-Sunday. \$20. 8 hrs. Contact: Birt Harvey, M.D., 1101 Welch Road, Suite A-1, Palo Alto 94304.

May 26-29—Symposium on the Infant at Risk: Early Detection and Preventive Intervention. Mt. Zion Medical Center and the National Foundation, March of Dimes at Jack Tar Hotel, San Francisco. Wednesday-Saturday. Multidisciplinary attempt to synthesize newest information concerning foetal, infant and child development in the crucial first three years of life. Genetic, cross-cultural, ecologic, nutritional, physiological, psychological and emotional aspects. Contact: Ruth Gross, M.D., Mt. Zion Hospital and Medical Center, 1600 Divisadero St., San Francisco 94115. (415) 567-6600.

June 4—Annual Premature Day. STAN. Friday. Neonatal intensive care and highlights of research.

June 10-12—Advances in Pediatrics. UCSF. Wednesday-Saturday. Adolescence, cardiovascular disease in infancy, nutrition, endocrinology, respiratory disease, immunization, neonatal emergencies, neurological problems, hypersensitivity disease, renal disease and genetic counselling. 17½ hrs.

June 14-17—Clinical Evaluation of Children with Learning Disorders. UCSF. Monday-Thursday. Physician's role in history, physical and neurological examination, academic achievement screening, family interview, interpretation of findings to the child and his family, working with family and school in formulating and following through on plans of management. \$110. 18½ hrs.

June 23-25—Annual Pediatric Seminar. Childrens Health Center at Sheraton Hotel, Harbor Island, San Diego. Wednesday-Friday. The Preschool Years. \$30. 16 hrs. Contact: David L. Chadwick, M.D., Medical Director, Childrens Health Center, 8001 Frost Street, San Diego 92123. (714) 277-5808, ext. 351.

July 12-14—Chronic Diseases in Childhood. STAN and American Academy of Pediatrics at Childrens Hospital of Stanford, Stanford. Monday-Wednesday. Recent advances in diagnosis and treatment of chronic diseases of childhood, improved techniques for the delivery of health services to children with chronic handicapping conditions. Sections on hematology, allergy, rheumatology, clinical immunology, chest diseases, anesthesiology, psychiatry, genetics, renology, radiology, endocrinology, gastroenterology. Contact: STAN.

August 7-8—Armchair Allergy. PMC. Saturday-Sunday. \$55.

September 18—Childrens Hospital Program. UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

Continuously—Pediatric Conference. Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. 1 hr. Contact: B. M. Kagan, M.D., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

#### Grand Rounds—Pediatrics

##### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

##### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

##### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

##### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

#### PSYCHIATRY

May 22—Managing Sexual Problems in Medical Practice. USC Division of Postgraduate Psychiatry at Airport Marina Hotel, Los Angeles. Saturday. 8 hrs. Contact: Donald H. Naftulin, M.D., Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

June 14-18—Community Mental Health and the Legal System. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

June 28-July 2—Comparative Psychotherapies. USC Division of Postgraduate Psychiatry at Newporter Inn, Newport Beach. Monday-Friday. \$50. 20 hrs. Contact: Donald H. Naftulin, M.D., Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

July 19-23—Legislative Issues in Community Mental Health. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

July 23-25—Workshops in Clinical Hypnosis and Hypnotherapy. American Society of Clinical Hypnosis at St. Francis Hotel, San Francisco. Friday-Sunday. \$125. 22 hrs. Contact: F. D. Nowlin, Exec. Sec., ASCH, 800 Washington Ave., Minneapolis 55414. (612) 331-9452.

July 26-30—Community Mental Health Planning for Services for Children. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

#### Grand Rounds—Psychiatry

##### Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

#### RADIOLOGY—PATHOLOGY

May 15—Gynecological Diseases. South Bay Radiology and Pathology Society at Little Village Theater, Carmel. Saturday. \$20. Contact: Robert M. Rinehart, M.D., Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262.

May 22-25—Disease of the Chest (Radiology Workshop). Northern California Radiologic Society and UCD at Sacramento Inn. Sacramento. Saturday-Tuesday. Contact: K. G. Ryan, M.D., Sec., NCRS, Woodland Clinic Medical Group, 1207 Fairchild Ct., Woodland 95695. (916) 662-4641.

June 7-19—Biological Electron Microscopy. USC at Allan Hancock Foundation Building, USC. Two weeks. Designed for professional and laboratory personnel desiring knowledge and experience in tissue preparation for examination with electron microscope. Contact: Dr. Robert F. Bils, Dir., Electron Microscopy Laboratory, USC. (213) 746-6015.

June 19-20—Advances in Clinical Enzymology and Other Laboratory Diagnosis. UCLA. Saturday-Sunday.



June 21-26—**Pathology of the Lung.** UCSD. Monday-Saturday. Pulmonary structure and function in relation to disease, pulmonary anomalies, emphysema, pneumonias, granulomatous diseases, pulmonary circulatory disturbances and vascular disease, hypersensitivity reactions and collagen diseases, neonatal and pediatric pulmonary pathology, tumors and tumor-like conditions of the lungs and pleura, miscellaneous pulmonary diseases of unknown etiology, methods for the study of pulmonary disease. \$200. 48 hrs.

June 27-July 2—**Society of Nuclear Medicine.** Biltmore Hotel, Los Angeles. Sunday-Friday. Contact: Margaret Glos, SNM, 211 E. 43rd St., New York 10017.

August 3-24—**Neuroradiology.** Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Tuesdays weekly. 8 hrs. Contact: J. Elizabeth Jeffress, M.D., Chief, Prof. Ed., Agnews State Hospital, San Jose 95114. (408) 262-2100.

Continuously—**UCSF Radiology Rounds, Seminars, and Conferences.** Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiology Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

#### Grand Rounds—Radiology-Pathology

##### Mondays

Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

##### Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

#### SURGERY—ANESTHESIOLOGY

May 17-21—**Le Roy C. Abbott Scientific Program and Samuel Higby Camp Annual Lectureship.** UCSF. Monday-Friday. Contact: Miss Terry von Wronski, Dept. of Orthopedic Surgery, HSE 641, UCSF. (415) 666-1126.

May 23-24—**American Laryngological Association.** Hilton Hotel, San Francisco. Sunday-Monday. Contact: Frank D. Lathrop, M.D., R.D. #1, Pittsford, Vermont 05763. (802) 483-6430.

May 23-25—**American Academy of Facial Plastic and Reconstructive Surgery.** Hilton Hotel, San Francisco. Sunday-Tuesday. Contact: Carl N. Patterson, M.D., Sec., 1110 W. Main St., Durham, North Carolina 27701. (919) 682-9341.

May 25-27—**American Laryngological, Rhinological, and Otological Society.** Hilton Hotel, San Francisco. Tuesday-Thursday. Contact: Louis E. Silcox, M.D., 108-11 Lankenau Medical Bldg., Philadelphia 19151. (215) 642-0136.

May 26-27—**American Broncho-Esophagological Association.** Hilton Hotel, San Francisco. Wednesday-Thursday. Contact: Walter Maloney, M.D., Sec., ABEA, 2065 Adelbert Rd., Cleveland 44106. (216) 791-7300.

May 28-29—**American Otological Society.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Wesley H. Bradley, M.D., 1100 E. Genesee St., Syracuse, New York 13210. (315) 476-3124.

June 3-4—**Highlights of Modern Ophthalmology.** PMC. Thursday-Friday. Cryosurgery, Current Trends in Corneal Surgery and Research, Glaucoma—Medical and Surgical Considerations and Medicolegal Problems, Photocoagulation of Macular Disease, Current Therapy of Diabetic Retinopathy, Modern Technology in Cataract Surgery, Fluorescein Fundoscopy, Recent Developments in Therapeutics, Retinal Detachment—The Buckling Procedures, Contact Lenses. \$125. 16 hrs.

June 12—**Painful Feet and Injured Ankles.** PMC. Saturday. 8 hrs.

June 19—**Clinical Electronystagmography Course.** Los Angeles Foundation of Otology. Saturday. Doctors urged to bring ENG technician. Anatomy and Physiology of Vestibular System, Demonstration of Techniques of Vestibular Stimulation and ENG Recording and Calculation, Significance of and Interpretation of Electronystagmogram, Vistas in Vestibular Investigation. \$60. 7 hrs. Contact: Jack L. Pulec, M.D., Los Angeles Foundation of Otology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

June 24-26—**1971 Stanford Ophthalmology Conference.** STAN. Thursday-Saturday. Present state of knowledge in fields of ocular motility and ptosis, strabismus. \$125.

July 6—**Annual Basic Science Course in Ophthalmology.** STAN. Eight and one-half weeks through September 3. Designed primarily for residents. Instruction, lectures and laboratory sessions, emphasis on application of basic science principles to clinical situations and disease conditions.

July 22-30—**Pacific Coast Oto-Ophthalmological Society.** Royal Hawaiian Hotel, Honolulu. One week. Contact: Francis A. Sooy, M.D., Dept. of Otolaryngology, UCSF.

July 26-28—**The Shoulder in Sports.** American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. \$150. 24 hrs. Contact: Fred Behling, M.D., 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

August 6-8—**Management of Anesthetic Problems in Medical, Obstetrical and Surgical Specialties.** UCLA at Neuropsychiatric Institute, UCLA. Friday-Sunday.

August 11-15—**Advanced Seminars in Urology.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

#### Grand Rounds—Surgery

##### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

## Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

## Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

## Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

## Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. USCD.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

## OF INTEREST TO ALL PHYSICIANS

### CMA Postgraduate Institutes and Circuit Courses

June 17-18—Sacramento Valley Counties Regional Postgraduate Institute. CMA, USC and Sacramento County Medical Society at Sahara-Tahoe Hotel, Lake Tahoe. Thursday-Friday. \$20. Infections, Immunizations, and Immunology. Contact: CMA.

May 15—Third Annual Symposium—Baldwin Hills Hospital. Proud Bird Restaurant, Los Angeles. Saturday. Refresher course for general practitioner. Medical emergencies in the office; cardiac shock, hematological emergency, cardiac emergency, drug interactions, respiratory emergency. 6½ hrs. Contact: Howard R. Bierman, M.D., Program Chmn., Baldwin Hills Hospital, 5525 W. Slauson Ave., Los Angeles 90056. (213) 645-2110.

May 22—Annual Seminar—General Hospital of Ventura County. Saturday. 4 hrs. Contact: J. Austin Daly, M.D., General Hospital of Ventura County, Ventura 93003. (805) 648-6181.

May 22—Medical Alumni Reunion Clinical Symposium. STAN. Saturday.

May 23—Office and Lab Orientation: A Symposium for Medical Assistants. UCSF. Sunday.

May 27—Medical Centers of Africa. USC in Senegal, Ivory Coast, Ghana, Uganda, Kenya. Three weeks.

June 13-17—Western Area Conference of Foundations for Medical Care. United Foundations for Medical Care Service Corporation at Kauai Surf Hotel, Lihue, Kauai, Hawaii. Sunday-Thursday. Contact: Norman A. Brown, Exec. Sec., 1625 Franklin Ave., Santa Rosa 95404.

June 30-July 4—Eleventh Annual Seminar for General Practitioners. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday. 24 hrs.

July 16-17—Effective Medical Communication. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Friday-Saturday. \$225.

August 14-25—Fourteenth Annual Postgraduate Refresher Course. USC at Sheraton-Waikiki, Tripler General Hospital, and Kauai Surf Hotel, Honolulu and Kauai. Two weeks.

August 30-September 2—American Hospital Association. Civic Auditorium, San Francisco. Monday-Thursday. Contact: Edwin L. Crosby, M.D., Exec. Vice-Pres., AHA, 840 N. Lakeshore Dr., Chicago 60611. (312) 645-9400.

September 15-17—Emergency Care. UCSF. Wednesday-Friday.

September 22—Cedars-Sinai Alumni Association Symposium. Century Plaza Hotel, Los Angeles. Wednesday. Contact: Mrs. Barbara Markell, Cedars-Sinai Alumni Sec., Cedars-Sinai Alumni Assoc., 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111.

Continuously—What's New Series. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Third Wednesday monthly. Contact: J. Elizabeth Jeffress, M.D., Chief, Prof. Ed., Agnews State Hospital, San Jose 95114. (408) 262-2100.

Continuously—Basic Science Correlation in Disease. VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.

Continuously—Ventura General Hospital Program. UCI and Ventura General Hospital at Ventura General Hospital, Ventura. Monthly lectures by UCI faculty. Contact: UCI.

Continuously—Postgraduate Medical Lecture Series—Orange County. UCI and Orange County Chapter, American Academy of General Practice at Saddleback Inn, Santa Ana. Monthly lectures by UCI faculty. June 4, Secondary Hypertension. Contact: UCI.

Continuously—Postgraduate Medical Lecture Series—Riverside-San Bernardino. UCI and Riverside-San Bernardino Chapter, American Academy of General Practice at Rams Horn Inn, San Bernardino. Monthly lectures by UCI faculty. May 21, Diagnosis and Management of Bleeding Disorders. Contact: UCI.

Continuously—Educational Tape Service for Orthopaedists, Rheumatologists. Orthopaedic Audio - Synopsis Foundation. Monthly recorded teaching program on C-60 cassette tapes available to orthopaedic surgeons, rheumatologists and resident physicians. Twelve monthly tapes, annual subscription rate of \$72 (\$50 for residents). Contact J. Tonn, Managing Editor, Orthopaedic Audio-Synopsis Foundation, 6317 Wilshire Blvd., Los Angeles 90048. (213) 986-0131.



**Continuously—Inter-Hospital Conference.** UCSD and participating hospitals in the San Diego area at Radiology main conference room, UCSD. Weekly conferences conducted by various hospitals. Consult UCSD for dates and participating hospitals.

**Continuously—Weekly Seminar for Graduate Students.** UCSD at Basic Sciences Building, UCSD. Weekly Wednesday seminars, open to interested physicians. 12 noon.

**Continuously—Dean's Day Program.** UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. May 27, Anesthesia; June 24, Neurology. Contact: UCSD.

**Continuously—Biomedical Lecture Series.** UCSD. May 19, 8:00 p.m., Basic Sciences Building, UCSD.

**Continuously—Basic Science Lecture Series.** UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

**Continuously—Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

**Continuously—Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malprac-

tice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MMN Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all California medical schools. Contact: Richard R. Getz, Exec. Dir., MMN, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

**Continuously—Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Practicing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Endocrinology, Metabolism, Gastroenterology, Hematology, Neurology, Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: April-May, June-July. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

**Continuously—Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, environmental radiation standards and nuclear power plants, overpopulation, abortion and contraception, technological problems of power generation in the United States, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and supersonic transport. Contact: John W. Farquhar, M.D., Assoc. Prof. of Medicine, STAN.

**Continuously—Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.



# The Prevention of Residual Biliary Calculi

J. MANNY SHORE, M.D., *Los Angeles*

■ *Residual calculi following cholecystectomy may be expected in approximately seven percent of cases. The vast majority of these are overlooked during operation; truly re-formed stones are rare.*

*Calculi are missed during cholecystectomy because of failure to explore the common bile duct. This is due to (1) the presence of silent choledochal stones, and (2) reliance on negative cystic duct cholangiograms in the presence of indications for common duct exploration.*

*Overlooking of silent stones during cholecystectomy may be prevented by routine operative cholangiography. Ideally, false-negative cystic duct cholangiograms should be eliminated by the use of fluoroscopic cholangiography.*

*Retained calculi following duct exploration may be prevented by (a) routine biliary endoscopy and (b) completion fluoroscopic cholangiography.*

*Re-formation of ductal calculi can probably be prevented by appropriate biliary drainage procedures performed during the initial choledochotomy. Selection of patients for primary biliary decompression remains an experimental problem.*

THE SURGICAL CURE OF BILIARY LITHIASIS requires removal of all calculi in the biliary tract and the correction of factors which may lead to recurrence. Both the overlooking of calculi at the time of cholecystectomy, whether or not the common duct is opened, and the new formation of calculi in the bile ducts after operation may be prevented by the utilization of advances in instrumentation and in choledochal operative techniques.

From the Department of Surgery, Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, Los Angeles.

Submitted revised, June 11, 1970.

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## Incidence

### *Retained Calculi Following Cholecystectomy*

The probability of overlooking stones in the bile ducts at the time of cholecystectomy may be estimated by considering errors in the usual procedural sequence. If there are no indications for choledochotomy, operative cholangiography is generally not done. Yet when it has been done in such circumstances, "unsuspected" calculi have been found in 4 percent<sup>1-15</sup> representing 2.4 percent of all cholecystectomies (Table 1). In patients with classical indications for common duct



TABLE 1.—*Potential Sources of Retained Calculi\**

Group	Percent of Cholecystectomies	Retained Stones	
		Percent of Group	Percent of Cholecystectomies
CHOLECYSTECTOMY, no indication for choledochotomy. . . . .	60	4	2.4
CHOLECYSTECTOMY, indication for choledochotomy. NEGATIVE OPERATIVE CHOLANGIOGRAM, no choledochotomy. . . . .	25	10	2.5
CHOLECYSTECTOMY, CHOLEDOCHOTOMY, completion cholangiogram . . . . .	15	8	1.2
			Total: 6.1

\* From Jolly<sup>12</sup>

exploration, choledochotomy is now commonly done if cystic duct cholangiograms are positive or suspicious. In patients whose ducts are not opened because cholangiograms show no abnormality, an error of approximately 10 percent has been shown by deliberate choledochotomy.<sup>5,12-16</sup> This represents an over-all error of 2.5 percent for all patients undergoing cholecystectomy (Table 1). Adding this error of false negative cholangiograms to the incidence of silent calculi detected by routine cholangiography, one can calculate that stones are retained in the bile ducts in 4.9 percent of patients undergoing cholecystectomy as commonly practiced.

#### *Residual Calculi Following Cholecystectomy And Choledochotomy*

**Retained.** Overlooked stones are found by postoperative cholangiogram in approximately 20 percent of patients when choledocholithotomy is done without operative cholangiography (Table 2). The addition of completion cholangiograms reduces this incidence by approximately 50 percent. The best results reported<sup>17,21</sup> probably reflect individual ability resulting from extensive experience in biliary operations, rather than any specific benefit of the procedures utilized.

**Re-formed.** There is little doubt that calculi can re-form in the bile ducts. This diagnosis can be made when large stones are removed several years following common duct exploration in patients with normal postoperative T-tube cholangiograms. Characteristically, the calculi differ morphologically from those found at the primary operation, being soft, non-faceted, with no central nidus and of an "earth-like"<sup>26</sup> consistency. The frequent detection of co-existing lesions interfering with biliary drainage further strengthens the conviction that these are re-formed calculi.<sup>26</sup>

Based on these criteria, the incidence of re-formed calculi after choledochotomy appears to be 4 percent.<sup>18,19</sup> This represents only 1 percent of all patients undergoing cholecystectomy.

The potential for residual (retained plus re-formed) calculi thus amounts to 7 percent of all cholecystectomies. This coincides with the reported incidence of residual calculi found in patients with the "post-cholecystectomy syndrome."<sup>28</sup> It should be emphasized that in the majority of patients with residual biliary calculi the common duct was not explored at the primary operation.

Reports indicate that from 30 percent to 83 percent of patients with retained calculi will become symptomatic, the majority requiring re-operation within the follow-up period.<sup>4,17,18</sup> Recurrence following re-operation exceeds that of primary operation, in addition to high morbidity and mortality rates. It therefore behooves the surgeon to make every effort to rid the biliary tract of calculi during the initial operation.

#### **Prevention**

##### *Retained Calculi Following Cholecystectomy*

**Routine operative cholangiography.** Operative cholangiography is by far the most valuable tool for the prevention of retained calculi. Objections to it on grounds of increased operating time and inaccuracy are readily dispelled as experience is gained with routine application.<sup>1-3,6-12,14,16,17</sup> Reports repeatedly indicate progressive improvement in results at a given institution with time and experience. Furthermore, the availability of a permanent record of common duct size at the time of cholecystectomy may be of inestimable value for comparison with future cholangiograms, in the event of post-cholecystectomy complaints.

The value of completion cholangiography fol-

TABLE 2.—*Incidence of Retained Biliary Calculi following Primary Choledocholithotomy Detected by Post-Operative Cholangiogram*

Author	Date of Report	No. of Choledocholithotomies	Completion Operative Cholangiogram	Biliary Endoscopy	Percent of Choledocholithotomies	Retained Calculi Mean Percent
Havard	1960	84	None	None	24	
Hicken <sup>17</sup>	1964	486	None	None	19	20
Johnston <sup>18</sup>	1954	153	Some	None	8	
Smith <sup>4</sup>	1957	123	Some	None	11	
Smith <sup>20</sup>	1963	166	Some	None	14	7
Colcock <sup>21</sup>	1964	139	Some	None	2	
Hight <sup>5</sup>	1959	77	All	None	9	
Hicken <sup>*17</sup>	1964	407	All	None	4	
Hicken <sup>**</sup>	1964	400	All	None	11	8
Fogarty <sup>***</sup>	1968	84	All	None	8	
Wildegans <sup>22</sup>	1960	143	All	All	3	
Schein <sup>23</sup>	1969	43	All	All	0	
Shore <sup>24</sup>	1969	100	Most	All	3	3
Weichel <sup>25</sup>	1969	233	All	All	3	

\* Author's personal series

\*\* Hospital Survey

\*\*\* Calculated from published data

lowing common duct exploration is generally accepted. Routine use of this procedure will lead to discovery of stones missed by exploration in approximately 10 percent of choledocholithotomies, thus reducing the incidence of retained stones by 50 percent (Table 2). However, this represents only 1.2 percent of patients undergoing cholecystectomy, since the duct is usually explored in only 15 percent of the cases. Routine operative cholangiography, the value of which is still questioned, regularly leads to the discovery of unsuspected calculi in 2.4 percent of patients undergoing cholecystectomy (Table 1). The advisability of performing an operative cholangiogram during every cholecystectomy is thus apparent.

**Operative cholangiography with television-fluoroscopy.** The classical indications for common duct exploration usually lead to unnecessary choledochotomy in more than 50 percent of cases. In recent years, several investigators have attempted to increase selectivity by the use of operative cholangiography.<sup>5,12,15,17,18</sup> While this has decidedly reduced the incidence of negative explorations, reliance on negative operative cholangiograms in patients with clinical indications for explorations has been associated with a false-negative incidence of approximately 10 percent. Letton<sup>10</sup> demonstrated that this source of error can be eliminated by an improved technique based on double contrast. Other approaches to increased cholangiographic accuracy involve the application of the image-intensifier to operative

radiology.<sup>30,31</sup> Appropriately designed operating tables, such as the Kifa, permit the use of a mobile image-intensifier with television monitor and a 70 x 70 mm roll-film camera, such as the Siemens. Operative cholangiography with this equipment incorporates the advantages of fluoroscopy and spot film technique, high resolution and improved communication between surgeon and radiologist.

#### *Retained Calculi Following Choledochotomy*

**Completion cholangiography with television-fluoroscopy.** Completion cholangiography as currently performed is associated with an 8 percent error (Table 2). It is expected that the use of this new technique, when applied to post-exploration cholangiography, will eliminate false-negative interpretation as a reason for leaving stones. While preliminary reports with this technique have been encouraging,<sup>31</sup> a statistical evaluation is yet to be done. The value of routine fluoroscopic operative cholangiography is currently under study at this institution. A higher degree of correlation between radiologic and surgical findings is expected.

**Biliary endoscopy.** In 1889, Thornton, performing the third recorded choledochotomy, inserted a Ferguson speculum into the distal common duct in order to visualize the ampulla of Vater.<sup>26</sup> In the intervening years, a variety of biliary endoscopes designed for this purpose have been described. None received wide ac-



TABLE 3.—Contributions of Biliary Endoscopy to Operation

Detection of overlooked calculi	22 percent
Aid to operation	6 percent
Assisted in removal of calculi	2
Assisted in operative decision	4
Aid to interpretation of cholangiogram	7 percent
Evaluation of "non-emptying"	1
Evaluation of filling defect	6

ceptance until the Wildegans rigid choledochoscope appeared in 1953.<sup>22</sup> Clinical experience with instruments of this type, mainly in Europe, brought enthusiastic reports. In this country, however, technical problems associated with the rigid construction have limited widespread adoption.<sup>32</sup> Dissatisfaction with the Wildegans endoscope led to the development of the flexible fiberoptic choledochoscope. The design, technique and results of clinical experience with this instrument have been recently reported elsewhere.<sup>24</sup>

Biliary endoscopy is performed through the choledochotomy incision following completion of choledochal exploration but before completion of cholangiography. The interior of the biliary tract, from the ampulla of Vater to the secondary divisions of the hepatic ducts can be clearly visualized. Calculi missed by conventional instrumental manipulation are readily detected and removed following endoscopy. Routine choledochoscopy led to the detection of such overlooked calculi in 22 percent of 100 consecutive cases of primary choledocholithotomy (Table 3) while failing to discover all biliary calculi in an additional 3 percent.<sup>24</sup> Similar results have been reported by other investigators (Table 2).

This combination of advanced technology in both operative radiology and endoscopy of the biliary tract will virtually eliminate the problem of the retained stone following choledochotomy.

**Other instruments.** Several instruments designed to improve the results of choledochotomy have been recently devised. The Fogarty biliary catheter is an extremely useful tool for operative evaluation of the distal common duct and ampulla, in addition to the removal of distal calculi. Its accuracy, however, is no greater than that achieved by operative cholangiography alone (Table 2). The ultrasonic probe, first described by Thurston and Kirby and recently revived by Eisman,<sup>33</sup> has similarly failed to surpass

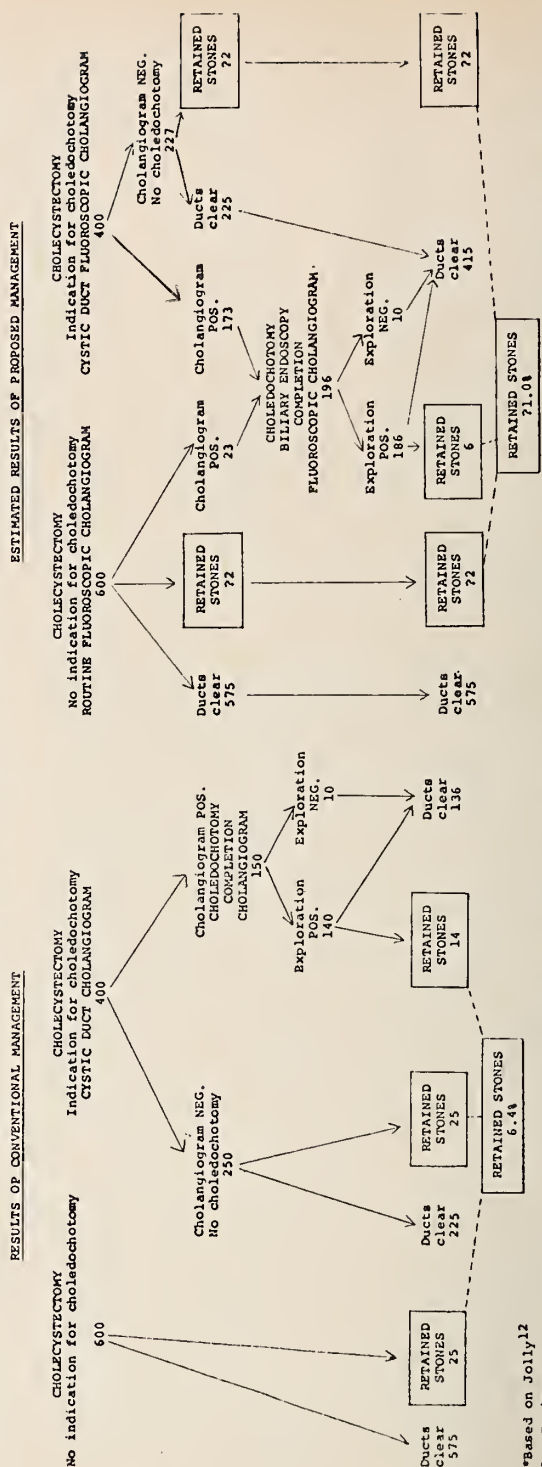


Chart 1.—Retained stones after cholecystectomy. Comparison of conventional and proposed management. 1000 consecutive patients with cholelithiasis.\*

TABLE 4.—Results of Procedures to Prevent Re-formed Calculi

Procedure	Reported by	Date	No. Cases	Mortality (percent)	Failure (percent)	Follow-Up (percent)	Years (Range)	Mean
Sphincteroplasty	Jones	1969	139	1	1	?	(½ to 15) . . . . .	5
Choledochoduodenostomy	Hurwitz	1964	40	2	2	94	(½ to 8)	
	Hess	1965	92	1	1	60	( 2 to 6)	
	Madden	1968	50	1	4	85	( 1 to 16) . . . . .	7
Sphincterotomy	Hess	1965	73	5	3	75	( 2 to 6)	
Hepatic Plexus Vagotomy	Schein	1969	15	0		Too early to evaluate		

Chart 1 compares results achieved by conventional management with those expected from the proposed methods. A six-fold decrease in the incidence of retained stones is anticipated. The use of routine fluoroscopic cholangiography should detect choledochal calculi usually overlooked during cholecystectomy, leading to choledochotomy in these patients. Retained stones will be found, then, mainly in patients whose ducts are not completely cleared following choledocholithotomy. This can be reduced to a minimum by routine biliary endoscopy and completion fluoroscopic cholangiography (Table 2).

#### Re-formed Calculi Following Choledochotomy

Biliary stasis is generally recognized as the underlying cause of re-formed calculi. When at the time of choledocholithotomy this is found to be due to a specific lesion, such as chronic pancreatitis, the need for a concomitant biliary drainage procedure is apparent. In many cases, however, the existence of biliary stasis is merely suggested by such findings as biliary mud, multiple calculi, pronounced dilatation of the duct, "primary" common duct stones,<sup>26</sup> or increased resistance to sphincter cannulation. In these circumstances, the addition of a primary biliary drainage procedure has been advocated to prevent re-formation of calculi.<sup>27,34,35</sup> While this has been accomplished with an acceptable mortality rate and favorable end results (Table 4), the relatively broad indications employed probably lead to excessive application. Furthermore, correlation between these indications and recurrence has not been documented by long-term studies.

The possibility of detecting potentially recurrent cases by more objective criteria has been evaluated by several investigators.<sup>27,35,37</sup> Elevated

passage pressures, as determined by operative biliary manometry, have been suggested as an indication for corrective procedures.<sup>36,37</sup> Jacobson<sup>38</sup> and others, however, found no correlation between manometric findings and clinical results. Their conclusions may be questioned, since they failed to assess pressure determinations by radio-manometry. Berci,<sup>39</sup> utilizing such studies, has shown that passage pressures recorded only by manometry may not be reliable determinants of outflow resistance.

The use of operative cholangiography with television-fluoroscopy will permit the documentation of valid passage pressures at operation as well as postoperatively. These findings can then be compared with long-term clinical evaluation. Correlation between increased outflow resistance and clinical recurrence could then identify cases requiring primary permanent biliary decompression. The prevention of re-formed stones thus remains an experimental problem.

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## PREOPERATIVE SYSTEMIC ANTIBIOTICS IN CHRONIC ULCERATIVE COLITIS

"In preparing a 'hypothetical 45-year-old male with an acute exacerbation of chronic ulcerative colitis for surgery, we note that he is febrile. This means that with his ulcerative colitis, he has mucosal inflammatory change and what probably amounts to a cellulitis of the bowel wall. In other words, he has an infection that cannot be reached by intraluminal antibiotics. It is our practice to give systemic antibiotics to all patients in this condition. I realize that there will be arguments on this score. But we have had much more success in decreasing the morbidity and mortality due to infection . . . by using some type of antibiotic regimen and beginning it about 24 hours before surgery.

"Our present choice of antibiotics in the patient with an infected colon is Keflin®. We give 2 grams every six hours, a total of 8 grams a day, 'piggy-back' intravenously beginning about 24 hours before surgery. To this we usually add ampicillin, 500 mg four times a day intramuscularly, again beginning the day before surgery. Ampicillin covers the range of anaerobes that Keflin misses. There are alternate programs. Some people use large doses—20 to 30 million units—of penicillin and I have no objection to this. . . . We have found Keflin uniquely free of side-effects, particularly as far as the kidney is concerned; and we have found ampicillin to be an extremely helpful adjunct."

—F. WARREN NUGENT, M.D., Boston

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# One to Two Year Treatment of Parkinson's Disease with Levodopa

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■ *One hundred patients with Parkinson's disease were treated with levodopa for more than a year at UCLA Medical Center. They were examined at given intervals and their improvement was graded. The optimum therapeutic dose was attained by balancing side effects against relief of symptoms and ranged from 1.5 grams to 8.0 grams per day (average 4.3 grams). There is no doubt that levodopa is the most effective treatment now available for Parkinson's disease. At the end of the first year, 60 percent of the patients improved 50 percent or better, and 10 percent were considered symptom-free. All major symptoms of this disease, including rigidity, akinesia and tremor, improved in variable degree.*

*There were no serious abnormalities in the routine clinical laboratory tests. The common side effects included nausea, vomiting and choreoathetoid dyskinesias. The side effects were not life threatening, but occasionally were major therapeutic challenges.*

*Maximal benefits with minimal side effects were achieved only by careful adjustments of the levodopa dosage as the months went by. This needed careful management by the physician and cooperation by the patient. Anticholinergic medications or amantadine hydrochloride, sometimes both, usually supplemented the effect of the levodopa.*

LEVODOPA (L-3,4-dihydroxyphenylalanine) can now be considered an established therapeutic agent for Parkinson's disease. In the decade it has taken to reach this stage, there have been at least five major episodes. (1) Dopamine was demonstrated in the mammalian central nervous system<sup>1</sup> and was shown to have the highest concentration in the striatum—the caudate nucleus

and putamen.<sup>2,3,4</sup> (2) Dopamine concentration was much reduced in the striatum and substantia nigra in Parkinson's disease.<sup>4</sup> Furthermore, Barbeau et al, in 1961, showed reduction of dopamine in the urine of parkinsonian patients.<sup>5</sup> (3) Several groups of Swedish investigators whose closely interlocking work was reviewed by Hillarp, Fuxe and Dahlström in 1966, demonstrated by histo-fluorescent technique a nigrostriatal neuronal pathway containing dopamine.<sup>6</sup> (4) Birkmayer and Hornykiewicz first showed in 1961 that intravenous dopa caused a clear but transient improve-

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ment in parkinsonian akinesia.<sup>7</sup> Possibly because the effects were mild, and also because of scepticism of new drugs in the treatment of Parkinson's disease, later studies with intravenous or small (we would now say) oral doses of levodopa either gave weak confirmation or reported no significant effect. (5) Cotzias et al, in 1967, reported that DL dopa in doses of 3 to 16 grams a day produced major and occasionally complete remission of parkinsonian rigidity and akinesia.<sup>8</sup> They reported less effective control of tremor. These results were accompanied by significant side effects: leukopenia in 4 of 16 patients. When the levo-rotatory form was used alone in large doses, beneficial effects were still striking and were not complicated by potentially serious side effects.<sup>9,10,11</sup>

The present report is based on a clinical study conducted at the UCLA School of Medicine during the past two years. This series consists of the first 100 patients to enter our treatment program. The patients now have been followed for one year to two years. The purpose of this report is to describe the therapeutic effects, side effects and treatment failures of levodopa in Parkinson's disease.

## Methods and Materials

The series consisted of 63 men and 37 women ranging in age from 40 to 78 years (average, 62). Ninety-two had Parkinson's disease (paralysis agitans) and seven were considered to have post-encephalitic parkinsonism. One patient had an associated en plaque meningioma and his parkinsonism was considered to be atypical. Forty-three of the patients had had previous stereotactic surgical operation for their illness. The duration of the illness for the entire group ranged from 2 to 46 years (average: 10.7).

In the first ten patients we started the administration of levodopa in the hospital. Thereafter we initiated the levodopa therapy in the outpatient clinic. A pretreatment evaluation consisted of a complete history and general medical and neurological evaluation to confirm the diagnosis and rule out any serious illnesses. The laboratory evaluation included a complete blood count, urinalysis, liver function studies (bilirubin, SGOT, LDH), renal function test (BUN), PBI, uric acid, Coombs test, chest x-ray film and an electrocardiogram. For the first three months, follow-up visits and laboratory tests were obtained every two weeks.

After an optimal dose of the drug was obtained, follow-up visits were at one- to two-month intervals.

In order to assess the improvement in patients taking levodopa, we used a two-part scoring system to quantitate the efficacy of the drug (Table 1).<sup>11</sup> The first part was a list of symptoms and signs. The second part was related to disability in performing various daily activities (bottom of Table 1). Answers to this part were obtained by questioning the patient. Each of the items in the two categories was then weighted on a 1 to 10 scale according to its importance and multiplied by a number related to the degree of severity of the symptom (0=absent, 1=present, 2=pronounced). This gave a possible maximum total score of 108 for the signs and symptoms and 112 points for functional disability. At each visit, the improvement was determined by taking the total score as calculated before therapy and subtracting a score at a given time, the remainder then being divided by the initial score to express the amount of improvement in percentage. For example, if a patient had an initial score of 90 and later it decreased to 40, then the remainder of 50 would be divided by the initial score of 90 and the improvement would be stated as 55.5 percent.

Anticholinergic agents were continued in those patients using them. After an optimal dose of levodopa was achieved, we attempted to discontinue these standard antiparkinsonian drugs.

At the beginning of the investigation we were excluded patients with various disabilities, such as hypertension or previous myocardial infarction. Later we included patients with diastolic pressure of less than 100 mm of mercury. A number had bundle branch block or previous compensated congestive heart failure. Patients with clinical evidence of active renal, endocrine, hepatic or pulmonary disease, malignant disease or psychosis were not accepted. We did not accept patients who were taking phenothiazines, thioxanthines, butyrophenones, phenylpiperazines, reserpine, monoamine oxidase inhibitors, or alpha methyl dopa because these drugs also act on the catecholamines and serotonin. However, later we used, without problems, phenothiazines in small doses to control nausea, and amitriptyline hydrochloride (Elavil®), imipramine hydrochloride (Tofranil®) and protriptyline hydrochloride (Vivactil®) to combat depression. Since pyridoxine reverses the effects of levodopa, we instructed our

TABLE 1.—*Specimen Sheet Showing Scoring Factors Used in Determining Effect of Levodopa Therapy\**  
(see text)

		<i>Control Rating</i> 0=absent 1=present 2=marked		<i>Rating at time of visit when taking levodopa</i> 0=absent 1=present 2=marked	
<i>Symptoms and signs</i>					
Rigidity	(7)	×	_____ = _____	×	_____ = _____
Tremor	(5)	×	_____ = _____	×	_____ = _____
Akinesia	(9)	×	_____ = _____	×	_____ = _____
Dementia	(8)	×	_____ = _____	×	_____ = _____
Postural Abnormality	(3)	×	_____ = _____	×	_____ = _____
Depression	(5)	×	_____ = _____	×	_____ = _____
Seborrhea	(2)	×	_____ = _____	×	_____ = _____
Sialorrhea	(2)	×	_____ = _____	×	_____ = _____
Blepharospasm	(2)	×	_____ = _____	×	_____ = _____
Masked Facies	(1)	×	_____ = _____	×	_____ = _____
Speech	(10)	×	_____ = _____	×	_____ = _____
<i>Activities</i>					
Dressing	(5)	×	_____ = _____	×	_____ = _____
Eating	(7)	×	_____ = _____	×	_____ = _____
Walking	(10)	×	_____ = _____	×	_____ = _____
Getting Out of Bed	(6)	×	_____ = _____	×	_____ = _____
Turning in Bed	(4)	×	_____ = _____	×	_____ = _____
Getting Out of Chair	(5)	×	_____ = _____	×	_____ = _____
Climbing Stairs	(2)	×	_____ = _____	×	_____ = _____
Use of Toilet	(6)	×	_____ = _____	×	_____ = _____
Bathing	(6)	×	_____ = _____	×	_____ = _____
Handwriting	(5)	×	_____ = _____	×	_____ = _____
			Total Control Value: _____	Total Value at Time of Visit: _____	

\*Improvement was computed by the following mathematical formula:

$$\frac{\text{Total Control Value} - \text{Total Value at Time of Visit}}{\text{Total Control Value}} \times 100 = \text{Percent Improvement}$$

patients to avoid any vitamin supplement containing B<sub>6</sub> and also foods that contain large amounts of that vitamin—all beans and peas, sweet potatoes, yams, wheat germ, wheat bran, vitamin-enriched bread, bacon and pork, avocado, nuts and most of the so-called health foods.

We started administration of levodopa in a 500 mg dose daily and increased it by the same amount every fourth day until a daily dose of 3.0 grams was reached. From then on, increases were made very gradually and adjusted individually. The dosage increase was carried to the point of maximum benefit with regard to symptoms, or until significant side effects occurred, or until a dosage of 8.0 grams a day was reached. The daily dose was divided into four or as many as six allotments. Concurrently, patients were encouraged to engage on a course of physiotherapy suited to their individual needs.

### Therapeutic Effects

First signs of improvement usually appeared after the second or third week of therapy. The patient himself often noted that he could turn in

bed more easily or had less tendency to hesitate while walking. As measured by our previously mentioned scoring method, more than one-fourth of the patients had improved 50 percent or more by the end of the first trimester (Table 2). At the end of six months, more than half had improved 50 percent or better, and by the end of the first year this degree of improvement had been attained by 62 percent of all patients who had started in the treatment program. At the end of 12 months 10 percent of the group were considered to be free of symptoms. This figure remained unchanged as long as they continued to take the prescribed medication. Only three patients were lost to the program, one because of intractable nausea and vomiting at a dosage of 1 to 1.5 grams of levodopa a day, another who relapsed to his former incapacity after initial improvement, and a third who died of congestive heart failure unrelated to the treatment of Parkinson's disease. A few patients continued to improve after six months; a few regressed because of side effects and inability to take large doses of the drug.



TABLE 2.—*Degree of Improvement in Patients Receiving Levodopa Therapy*

<i>Time of Exam</i>	<i>No. of Patients</i>	<i>Treatment Stopped*</i>	<i>Worsened</i>	<i>0-24 (percent)</i>	<i>25-49 (percent)</i>	<i>50-74 (percent)</i>	<i>75-99 (percent)</i>	<i>100 (percent)</i>
3 months	100	0	1	31	31	19	16	2
6 months	100	1	0	15	27	25	22	10
12 months	100	3*	1	10	24	29	23	10

\*Means the figure is cumulative from previous examination period.

TABLE 3.—*Percentage Improvement in Individual Signs, Symptoms and Daily Acts of Living*

	<i>3 Months</i>	<i>6 Months</i>	<i>12 Months</i>
Rigidity	45	66	62
Tremor	28	42	45
Akinesia	42	42	68
Dementia	29	48	51
Postural Abnorm.	13	33	55
Depression	53	52	58
Seborrhea	48	58	60
Sialorrhea	65	79	79
Blepharospasm	62	73	73
Masked Facies	43	53	74
Speech	33	40	47
Dressing	29	28	38
Eating	49	59	61
Walking	34	47	46
Out of Bed	36	60	60
Out of Chair	47	63	64
Stairs	39	50	51
Toilet	56	65	56
Bathing	32	47	49
Handwriting	26	44	52

Improvements in individual factors were variable. In evaluating three major signs and symptoms of Parkinson's disease we found that relief from rigidity was greatest early in the treatment, as shown in Table 3. At the end of the year, however akinesia was improved most (68 percent), rigidity next with 62 percent and tremor least with 45 percent.

The optimal daily dose represented a balance between limiting side effects, such as involuntary movements which developed at high levodopa doses, and maximum benefit as judged by the investigator. It ranged between 1.0 and 9.0 grams per day (average: 4.3). In individual patients, this optimal dose decreased or increased by one or two

grams per day over the year. In some patients choreoathetosis developed (see below under side effects) and their daily dose had to be reduced; in others, improved tolerance permitted an increase.

We have also found that anticholinergic drugs were complimentary with levodopa in the treatment of Parkinson's disease. Before the initiation of therapy, 87 of our patients were taking anticholinergic drugs and five took amantadine hydrochloride. During the year, these drugs were discontinued two or three times and were started again only if the patient was clearly deriving some benefit from them. By the end of the first year, there were still 60 patients who continued taking one of the anticholinergic preparations. Most commonly the reason for this was that it was contributing to the reduction of tremor. Other patients who attempted to discontinue these drugs found moderate worsening of their other signs and symptoms. Similarly, in a few of the cases amantadine hydrochloride complimented the effectiveness of levodopa.

One of the factors which appeared to have an effect on the degree of improvement with levodopa was the severity of illness. This is brought out in Table 4. All patients who had 100 percent improvement came from the moderately impaired group and none from the severely affected group. The latter group also rated poorer in over-all improvement, since more than half did not achieve even a 50 percent improvement and it also included the only patient who became worse during the treatment. These criteria, however, do not measure the significant benefit in an individual. A patient who had been totally disabled and then became able to feed himself and walk with

TABLE 4.—*Severity of Parkinson's Disease and Improvement After 12 Months*

	<i>Treatment Stopped</i>	<i>Worsened</i>	<i>0-24%</i>	<i>25-49%</i>	<i>50-74%</i>	<i>75-99%</i>	<i>100%</i>
Mild	0	0	0	0	1	1	0
Moderate	1	0	6	13	18	16	10
Severe	2	1	4	11	10	6	10

**TABLE 5.—Side Effects**  
(Severe side effects are given in parentheses)

	Duration of Therapy			Total
	3 Months	6 Months	12 Months	
Nausea and/or Vomiting	36(2)	18(1)	7(0)	43(3)
Anorexia	4	1	0	5
Postural Hypotension	7	2	2	9(0)
Flushing	0	0	0	0
Dyskinesias	21(2)	24(3)	8(2)	38(4)
Mental Disturbances	4	2	0	5
Organic Confusion	5	3	0	6
Cardiac Disturbances	4	2	0	4
Palpitation	4	2	0	4
Dysrhythmias	0	0	0	0

some difficulty may have improved less than 25 percent on our grading scale, yet to him these improvements were of considerable importance.

Other factors such as age, duration of illness, cause of disease, and previous stereotaxic brain operations did not influence the therapeutic effect of levodopa. On the other hand, the presence of organic dementia or of depression reduced the likelihood of pronounced improvement.

## Side Effects

The incidence of side effects is listed in Table 5. These include nausea, vomiting, anorexia, involuntary movements, postural hypotension and cardiac disturbances. Nausea and vomiting most commonly occurred in the morning and were a problem at some stage in almost half of the patients. For the most part these symptoms subsided with time. One patient had to discontinue levodopa because of intractable nausea and vomiting. The incidence of nausea and vomiting could be reduced by slowing the rate of increase of levodopa, by taking the drug with food, or by dividing the daily dose into smaller amounts. Sometimes taking an antacid before the levodopa tablet helped. In several patients, a phenothiazine (Compazine®) was useful. We also tried to de-emphasize the side effects of nausea and vomiting in the patients mind, as we have observed that these symptoms can be due to placebo alone.

When higher doses were reached, some patients again had nausea and vomiting. Reducing the dosage by 0.5 or 1.0 grams usually controlled these symptoms. Anorexia, accompanied by some weight loss was seen in four patients early in the treatment and in one late in the treatment.

The involuntary movements, best characterized

as choreoathetoid or dystonic, appeared in 38 patients. At the end of one year they were present in eight patients, severe in two. They consisted of undulating movement of the tongue, head-bobbing, mouthing movements and head-turning. Less commonly there were jerking movements of the arms or legs. In a few patients, rhythmic contractions of the thorax and abdomen made respirations shallow and rapid. These movements were often exaggerated by volitional movements of other parts of the body.

The involuntary movements sometimes appeared in the first few months of levodopa therapy, but sometimes not until the sixth to the twelfth month. They seemed to be characteristic of patients with Parkinson's disease, since they did not appear in six normal controls used early in the study or in patients with other movement disorders such as spasmodic torticollis or dystonia musculorum deformans. When abnormal movements occurred, they could usually be controlled by reducing the daily dose by 0.5 to 1.0 gram. Several patients benefited by a reduction in levodopa dosage and the addition of a phenothiazine or imipramine hydrochloride. However, two patients have been on a borderline between inadequate control of Parkinson's disease and incapacitating choreoathetosis.

Postural hypotension was defined as a drop in blood pressure of 30 mm of mercury on assuming an upright position or a fall of systolic blood pressure below 100 mm. It occurred in nine patients, some of whom complained of dizziness in upright posture. None of the patients fainted, although fainting has been reported by other investigators.<sup>12</sup> These patients were severely disabled with Parkinson's disease, particularly akinesia and rigidity, and most of them were depressed. The postural hypotension was reduced by either decreasing the levodopa a modest amount or by use of elastic stockings. It usually cleared after several months. We did not use fludrocortisone acetate (Florinef®) for hypotension although other investigators<sup>11</sup> have.

Mental disturbances, as found in five patients, consisted of insomnia, depression and euphoria. Depression usually predated the use of levodopa. These patients did not have any organic dementia. There were six other patients who exhibited clear organic mental disturbances, five early and one late. It persisted in two of them during the



TABLE 6.—Comparison of Patients Considered Treatment Failures With Those With 100 Percent Improvement

Pt.	Age	Sex	Duration of Illness	Disability Rating Before Rx	Percent Improved	Main Symptom	Optimum Levodopa Dose	Side Effects	
								Dyskinesia	Nausea or Vomiting
1	69	M	7	176	20	A	7.5	—	—
2	70	M	7	131	20	A	8.0	—	—
3	70	F	10	95	8	A;R;T	6.0	—	Moderate
4	61	F	9	121	18	A	3.0	Mild	Severe
5	62	M	7	102	22	A;R	7.0	—	—
6	68	M	9	113	9	A;T	5.5	—	Moderate
7	74	F	8	88	100	R	2.0	—	—
8	63	M	13	86	100	R;A;T	4.0	—	Mild
9	61	M	11	91	100	R;A;T	3.0	Mild	—
10	58	M	5	98	100	R;A;T	5.0	Mild	Mild
11	42	M	4	60	100	T	5.0	Mild	Mild
12	62	M	22	112	100	R;A;T	5.0	—	Mild
13	53	M	7	77	100	R;A;T	4.5	Mild	—
14	62	M	4	38	100	R;A	3.5	Mild	—
15	44	M	6	60	100	R;A	7.0	—	—
16	74	F	5	43	100	R;A	2.5	—	Mild

A = Akinesia. R = Rigidity. T = Tremor.

full year. In these cases, confusion, hallucinations and agitation were prominent. Most of these patients had some organic dementia before therapy. Depression was successfully treated by the usual recommended therapeutic doses of amitriptyline (Elavil®), imipramine (Tofranil®), or protriptyline (Vivactil®) while continuing the levodopa at previous dosage levels.

In none of the cases in our series did we note the cardiac dysrhythmia reported elsewhere,<sup>10,11</sup> although four patients have complained of heart palpitations, frequently occurring after ingestion of large doses of the drug.

Sexual performance improved only in relation to the improvement in mobility and well-being and no aphrodisiac effects were observed.

There was one death in our group. The cause was congestive heart failure and there was no evidence it was related to levodopa therapy.

There were few biochemical abnormalities observed. There were no instances of protein-bound iodine elevation. No leukocytosis or leukopenia were noted. Positive reaction to Coombs test developed in four patients during therapy, but no hemolytic abnormality was demonstrated. Transient BUN elevations with values from 22 to 35 were seen in 15 of the patients. Creatinine determinations remained normal. Degradation products of levodopa frequently resulted in change of urine color to deep amber, especially on standing, and also resulted in positive urine tests for acetone and diacetic acid. Serum transaminase elevation due to impaired gastrointestinal absorption or re-

was noted in seven patients, but this also was transient and mild. Normocytic, normochromic anemia with hematocrits of 28 and 30 occurred in two patients, but no explanation for this could be found. None of these laboratory abnormalities necessitated reducing or discontinuing levodopa.

## Discussion

The data we have presented is comparable to that of other reported series.<sup>10,11</sup> There were individuals who showed pronounced improvement, others who responded rather poorly. Comparing and contrasting some of the factors in Table 6 brings out some interesting features. It is apparent that those who had no symptoms at the end of the first year of treatment were relatively less disabled at the beginning of therapy. There was no difference in age or duration of illness between the two groups. However, the poorly responsive group of patients had severe akinesia as compared with other patients. The average levodopa dose for the group which responded poorly was much greater (5.1 grams) than for the entire study group or select symptom-free group (4.3 grams). Since all the patients had the levodopa dosage pushed to the point of significant side effects or to a level of 8 (or rarely 9) grams a day, this indicates these individuals were able to tolerate larger than usual amounts of the drug. One can perhaps speculate that those who responded poorly, despite high doses of levodopa, did so because their central dopamine levels were never high. This may be related to transport across the blood brain barrier.

The efficacy of levodopa in Parkinson's disease based on one year's experience is unequivocal. It is the best treatment we have found for parkinsonism. Its clinical effect is due to, and has in turn produced considerable interest in monoamine research. At the same time, it is not an ideal medication. Its side effects, while not life-threatening, may be persistent and troublesome. The dosage administered is very high considering the small amount which is presumably active in the central nervous system.

Many questions remain. Does levodopa retard the progression of the disease by reducing the rate of dying of nerve cells in the substantia nigra which are responsible for dopamine production? Or does the large amount of therapeutically administered levodopa simply allow the remaining cells in the nigra to perform the dopa-to-dopamine decarboxylation more easily, while the gradual cell death goes on? There is some evidence to suggest that patients with virtual absence of nerve cells in the substantia nigra do not have therapeutic response to levodopa.<sup>12</sup> Clinical trials followed by post-mortem examinations for five to ten years will be necessary to resolve this issue.

The choreoathetoid dyskinesia induced by levodopa is a unique movement disorder and is also of interest. So far, we have seen it occur only in parkinsonian patients. It appears that an underlying cellular and biochemical alteration specific to these patients may be an important factor in these involuntary movements. The narrow dosage boundary between effective therapy and development of choreoathetosis suggests the same biochemical pathway is involved to a different degree. Yet, other possibilities have to be considered. For example, serotonin depletion may be a factor, since levodopa, when administered in large amounts, may depress serotonin and serotonin metabolites,<sup>13</sup> possibly by utilizing the decarboxylase common to both dopamine and serotonin formation.

Why do a few patients relapse after several months of pronounced improvement? Possibly another site of dopa-to-dopamine conversion, such as the brain capillary endothelium,<sup>14</sup> has started utilizing all of the dopa destined for the central nervous system. Possibly a relative deficiency of adenosylmethionine, a donor of the methyl groups necessary at several stages in dopamine metabo-

lism,<sup>15</sup> is a factor. These questions should be answerable by animal and possibly human experimentation.

Turning again to the clinical side, we can say levodopa is an interesting and challenging drug to the physician to administer and is liable to give the parkinsonian patient significant benefit if he can reach and continue taking an adequate daily dose for the first few difficult months. From that time on, the patient usually needs no persuasion to continue the drug. We still use the principal dosage-regulating techniques and means of combating side effects noted earlier in this paper. Since no serious changes in the results of laboratory determinations have been noted, we now order routine blood studies, urinalysis, BUN and SCOT at the beginning of therapy and repeat these at three- to six-month intervals.

Since levodopa is likely to significantly help even bedridden invalids with Parkinson's disease, it seems wise to give a four- to six-month trial to most such patients. We would avoid only those incapacitated patients with a severe degree of dementia.

Patients with very mild parkinsonism of one to two years duration represent another problem. We don't yet know whether levodopa has only a suppressant action on parkinsonian symptoms or has some curative action. The latter appears unlikely, but it is a possibility. Levodopa is a troublesome medicine to take, and is still quite costly. In view of these and other factors, we have not been giving levodopa in the very mild cases unless the patient badly wants the drug and plans to continue taking it for many years to come, probably the rest of his life.

There is wide variation in patient responses to levodopa. In view of this, the physician's directions to the patient, within the confines of the dosage-regulating techniques noted above, must be very flexible. For the first year of therapy, and especially for the first few months, the physician must be readily available, willing to make suggestions over the phone, offer encouragement, make repeated minor dosage adjustments, be willing to improvise, to learn to anticipate certain of the side effects, and to see the patient promptly if indicated. These cautions should not make the physician avoid using levodopa; rather, he should approach the drug with the respect he gives to the use of other potent drugs such as dicumarol.



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# The Activated Coagulation Time of Whole Blood as a Routine Pre-Operative Screening Test

PAUL G. HATTERSLEY, M.D., *Sacramento*

■ *Patients with disorders of hemostasis who undergo surgical procedures are in danger of hemorrhage. While the careful medical history remains the most sensitive test of a bleeding tendency, some such patients can give no suggestive history. In three patients with coagulopathy—one with mild classical hemophilia, one with Christmas disease, and one with warfarin toxicity—the abnormality was missed by routine preoperative history but promptly detected by the routine preoperative use of the activated coagulation time (ACT). Either this test or the activated partial thromboplastin time should be included in the routine preoperative work-up, along with appropriate additional tests of the hemostatic mechanism.*

PROBABLY VERY NEARLY one person in a thousand has a congenital disorder of the hemostatic mechanism. The minority of them have obviously severe coagulopathic conditions, their histories replete with bleeding episodes. Many more of them have milder disorders. Some can give no personal or family history of abnormal bleeding. Yet all of these persons, as well as the many with acquired hemostatic disorders, are in some hazard if they undergo an operation without recognition and appropriate handling of their disordered hemostasis.

A simple preoperative study should uncover the vast majority of these potential bleeders. Yet routine preoperative laboratory screening for bleeders has fallen into wide disrepute. Much of this disrepute doubtless stems from the well-established insensitivity of the Lee-White coagulation time, which for many years was everyone's routine screening method. Many

physicians do not recognize that, without downgrading the importance of the careful preoperative history, modern medicine can now offer much more sensitive and reliable tests of the hemostatic mechanism, and can perform them at relatively little expense in time and materials.

This paper will report upon three patients with potentially dangerous coagulopathic conditions which were missed completely by preoperative history, and were immediately detected by bedside use of a routine activated coagulation time of whole blood (ACT).

## The Activated Coagulation Time (ACT)

The author originally modeled the activated coagulation time of whole blood (ACT)<sup>1</sup> after the activated plasma recalcification and partial thromboplastin time techniques of a number of workers. It is a simple bedside test in which whole blood is massively contact activated by drawing it directly onto diatomaceous earth. We found a mean clotting time, when observed at 37° C, of 1 minute and 47 seconds (1'47"). The times in five thousand normal subjects presented a very acceptable bell-shaped curve of

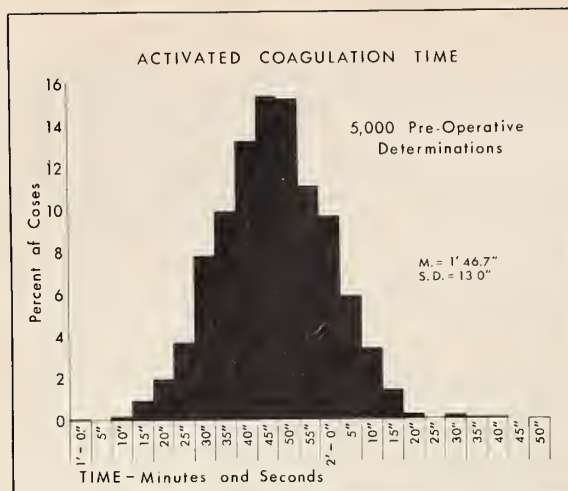
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distribution (see chart). The standard deviation in this group was 13 seconds, giving a 95 percent range (Mean  $\pm$  two standard deviations) of 1 minute and 21 seconds (1'21") to 2 minutes and 13 seconds (2'13"). We found the test quite precise and reproducible, with a coefficient of variation, on duplicate determinations, of 4.5 percent in the normal range.

We at that time reported the ACT sensitive to factor VIII (AHG) deficiencies up to 25 percent of normal, whether due to classical hemophilia or von Willebrand's disease, but somewhat less sensitive to factor IX (PTC) deficiency. We had found it very sensitive to deficiency of factor XII (Hageman), and it had readily detected severe depression of vitamin K-dependent factors in patients receiving hypoprothrombinemic drugs, and in those with severe liver dysfunction. It had on a number of occasions demonstrated the coagulation defect of intravascular defibrination syndrome, and had proven a valuable and time-saving substitute for the Lee-White test in the control of heparin therapy. We have also used it extensively in the control of anti-hemophilic therapy.<sup>2</sup>

Since its original description, tens of thousands of these tests have been performed in many centers, the normal values remaining unchanged. Djerassi,<sup>3</sup> in a personal communication, reported detecting factor XI (PTA) deficiency with a modification of this test, and Brittin<sup>4</sup> similarly described a patient with isolated deficiency of factor X (Stuart-Prower factor), which the ACT readily demonstrated. The

test has likewise proven very sensitive to deficiency of the Fletcher factor.<sup>5</sup> Our own experience<sup>6</sup> indicates that it will not detect the moderate fibrinogen deficiency of heterozygous fibrinogenopenia, although the characteristic soft clot after retraction suggests the diagnosis. We as yet have no information regarding the sensitivity of the ACT to the rare single deficiencies of factors V (proaccelerin) or VII (proconvertin), or of prothrombin.

## Methods

In performing the ACT, we have followed exactly the technique originally described,<sup>1</sup> drawing 2 mm of blood by the second tube technique into a warm, evacuated tube containing 12 mg of diatomaceous earth\*, incubating the tube at 37° C in a heat block or small vacuum bottle, tipping it each five seconds after the first minute, and recording the time of appearance of the first definite clot. Times over 2'10" we have considered presumptively abnormal, indicating need for further study of the blood and the patient. We have usually performed the test in duplicate; and technologists, technologist trainees, nurses, medical students and interns, after a minimum of experience, have encountered little difficulty in reading the end-point or in obtaining good agreement between their paired observations.

With the ACT in preoperative screening, we have routinely determined the bleeding time by the Duke method,<sup>7</sup> to detect those disorders of hemostasis not related to defects of the intrinsic coagulation cascade. We have also scanned a stained blood smear for adequacy of platelets, and have observed the ACT tube after overnight incubation at 37° C, to evaluate clot retraction and fibrinolysis. We have considered this a minimal screening series for hemostatic disorders in preoperative patients.

When we have encountered a prolonged ACT in a preoperative patient, we have followed it with further investigation. For such studies we have drawn nine volumes of venous blood into one volume of 0.1 Molar acid citrate\*\* solution in a plastic tube. We have used the one-stage prothrombin time (PT) of Quick;<sup>8</sup> the "P & P" test of Ware and Stragnell;<sup>9</sup> the thrombin time

\* Celite (TM), Johns Manville Co. Evacuated tubes available from Becton-Dickinson and Co., Tube #3206 XF136.

\*\* Mixture of three parts of 0.1 M Sodium citrate and two parts of 0.1 M citric acid.

(PT) as described by Hardisty and Ingram;<sup>10</sup> the quantitative fibrinogen technique of Cullen and Van Slyke;<sup>11</sup> and the kaolin activated partial thromboplastin time (PTT) of Proctor and Rapaport.<sup>12</sup> For further diagnostic tests we have used the PTT and PT techniques on equal mixtures of patient's plasma with normal plasma, with citrated plasma of patients with known severe coagulation defects, or with artificially prepared deficient plasmas. In selected cases we have performed single factor assays, or sent plasma specimens to referral coagulationists for such tests.

#### *Case 1—Mild classical hemophilia with intracranial hemorrhage*

A 20-year-old college basketball player entered the hospital because of confusion, headaches, nausea and vomiting, all coming on shortly after a heavy fall. Reliable history proved impossible because the patient was in a semi-stuporous state and his family lived in another city. Under observation, signs of increasing intracranial pressure developed, with incoordination of the left arm and leg, and nystagmus. The neurosurgeon considered craniotomy.

On routine preoperative study, we found the bleeding time, platelets and clot retraction normal, but the ACT definitely prolonged (2'55", 3'00"). We also found a prolonged PTT (64 seconds), corrected by mixture of his plasma with an equal volume of plasmas severely deficient in factors IX, XI and XII, but not by plasma deficient in factor VIII. The factor VIII assay, performed for us elsewhere,\* was 11 percent of mean normal. We immediately infused eleven units of cryoprecipitates, as prepared by the technique of Pool and Shannon.<sup>13,14</sup> (One unit = precipitates from 450 ml of donor blood). A few minutes later we found the ACT mid-normal (1'40"), further supporting our diagnosis of mild classical hemophilia.

The patient subsequently received eight units of cryoprecipitates each eight hours for 10 days. His ACT remained normal during this period, although his plasma fibrinogen rose to 850 mg per 100 ml, presumably due to the large amount of fibrinogen in cryoprecipitates. (See Hattersley and Dimick.<sup>5</sup>)

Signs of intracranial pressure gradually subsided, making surgical interference unnecessary, and the patient left the hospital four weeks after

admission, with only mild residual neurological signs. Six months later he returned to college, apparently completely well. At that time we found an ACT of 3'10" and an activated PTT of 64.6 seconds, essentially the same as before treatment.

The parents, when finally contacted, said that the boy had been considered a "bleeder" as a child, and that two maternal uncles had likewise had bleeding problems. They had withheld this information from him.

#### *Case 2—Mild "Christmas disease" with minor operation*

An 11-year-old boy entered the hospital for removal of a small angioma from the anterior chest wall. The mother, in response to questioning by the surgeon, denied that the boy had ever bled abnormally, although he had had teeth extracted. Routine pre-surgical tests showed a normal bleeding time, clot retraction and platelets, but a slightly prolonged ACT in duplicate (2'45", 2'35"). Further investigation showed a normal Quick prothrombin time and thrombin time, but a somewhat prolonged PTT (53.5 seconds), corrected by an equal mixture with plasma deficient in factor VIII, but not by factor IX deficient plasma. We subsequently obtained a factor IX assay of 6.3 percent,\*\* confirming our impression of mild Christmas disease.

The surgeon cancelled the elective procedure and carefully re-questioned the patient's mother, who eventually admitted that the boy had on two occasions bled badly following tooth extractions, and once following a scalp laceration. She had purposely withheld this information for fear that it would prevent the operation on her son.

On readmission of the patient, the ACT remained prolonged at 2'45" and 3'00", but infusion of 750 ml of fresh frozen plasma brought it to mid-normal (1'45"). The surgical procedure proved uneventful, with minimal bleeding, the lesion proving to be a benign hemangioma. The boy went home on the second postoperative day.

#### *Case 3—Warfarin toxicity*

A 45-year-old woman entered the hospital for extraction of 16 teeth. The oral surgeon called in a physician consultant, who failed to elicit

\*Courtesy of Judith B. Pool, Ph.D., Coagulation Laboratory, Stanford University School of Medicine, Stanford.

\*\*Courtesy of Sylvija Hoag, M.D., Hematology Research Laboratory, Children's Hospital of San Francisco.



any story of abnormal bleeding. We found the routine preoperative ACT definitely prolonged, however (3'45", 3'40"), the bleeding time, platelets and clot retraction normal. On our recommendation, the oral surgeon delayed his procedure for further investigation.

Further study demonstrated prolongation of the Quick prothrombin time (30" = 15 percent; control: 13"), of the P & P test (58" = less than 10 percent; control: 22"), and of the activated PTT (80").

More careful clinical history revealed that this patient with chronic rheumatic heart disease had undergone an open heart operation a year before for placement of a prosthetic aortic valve. She had received sodium warfarin since, recently taking 10 mg and 12.5 mg on alternate days. She had not mentioned anti-coagulant therapy to her questioner, who had not asked her specifically about it.

In preparation for operation, the patient received two injections of vitamin K-1 oxide, 10 mg each. Within two days the prothrombin activity had risen into the safe range for an operative procedure (Quick: 15.2 sec = 62 percent; P & P: 26 sec = 70 percent). The extractions went smoothly, without excessive bleeding, and the patient recovered without difficulty. She subsequently again received sodium warfarin.

## Discussion

Our experience with these three patients, and with many others like them, has confirmed our conviction that taking a patient to surgery without laboratory screening for coagulation defects poses definite risks. The patient may be confused or disoriented (as in Case 1 reported herein) or he may be ignorant of the facts. The person supplying the history may be unwilling to disclose the facts (as in Case 2). Some small

children with hemostatic disorders have never bled abnormally simply because they have never met sufficient hemostatic challenge to bring their bleeding tendency to light. Finally (as in Case 3) even astute physicians sometimes do not take a complete history. Hence the history alone may at times fail to detect important hemostatic defects.

After many thousands of determinations in our laboratories, the activated coagulation time of whole blood (ACT) has in our opinion thoroughly established its usefulness. When performed at 37° C as described, this simple bedside test has proven comparable in sensitivity to the activated PTT. We feel that one or the other of these two tests belongs in every routine preoperative work-up, along with a careful history. We also urge use of a sensitive bleeding time determination, screening of the smear for platelets, and observation of the incubated clot for clot retraction and fibrinolysis.

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# Medical Aspects of Violence

PHILIP SOLOMON, M.D., AND SUSAN T. KLEEMAN, M.D., *La Jolla*

■ *Physicians see violence in beaten wives, battered children, rage reactions, murder, and suicide. They should recognize that it may be a symptom of disease if it is unprovoked or bizarre, or is associated with impaired consciousness, confusion or irrationality. Violence in episodic trance-like states suggests limbic disease (temporal lobe lesions, psychomotor epilepsy, or "dyscontrol syndrome"); in association with personality change, dementia, or psychosis, it indicates cortical disease (structural, toxic, or idiopathic).*

PUBLIC HEALTH WORKERS have good reason to be concerned about violence. Federal Bureau of Investigation statistics for 1968 in the United States<sup>1</sup> show 13,650 murders, 31,060 forcible rapes, 282,400 aggravated assaults, 261,730 robberies, and well over half a million instances of criminal violence in all. On the highways in the United States where a man's power is amplified by 40 to 400 horses, a death occurs every ten minutes (more than 60,000 a year), and an injury every 17 seconds (three million a year). About 40,000 persons commit suicide each year in the United States.<sup>2</sup>

Physicians see the effect of violence in the care of individual patients—battered children, beaten wives, mayhem done by men to one another. Accident Floor surgeons work day and night with hemostats, needles, and catgut. Family doctors respond to emergency calls for poisonings of many sorts, deliberate, accidental and iatrogenic. Neurologists or psychiatrists may be called in if there are repeated episodes of violence and someone suspects associated organic brain disease or mental illness. Specialists in any field may encounter the results of violence when the organs

of their field are traumatized. All physicians should recognize that violent behavior may be a symptom of disease, like cough or fever, and its cause should be determined if possible.

## Maturational Levels

Children are not born with fully developed controls for emotional behavior. They must learn to crawl before they walk and walk before they run. Similarly, they must learn to check their impulses to cry or rage at frustration, postpone gratification, compromise, bargain, accept substitutes, and even surrender once in a while—that is to say, acquire will power. Children often assault one another under conditions of routine play. Rarely do these assaults result in serious injury and then usually by accident. The child who makes deliberate, vicious attacks on other children or animals is probably brain-injured or otherwise abnormal.

At adolescence, with myelinization in the central nervous system (CNS) largely completed (with resultant insulation and specialization of function) most children have acquired enough controls over their instinctual and libidinal impulses to warrant being called civilized. From then on it is civilization that conditions their violence. A few adolescents remain uncommitted and unre-

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constituted and continue to function emotionally as young children.

Normal adult human beings react vigorously when sufficiently provoked. A man attacked by ruffians may have to defend himself and counter-act. It is not violence when groups of men on a playing field crash into one another in a struggle over the direction of an elongated leather-covered ball. But repeated destructive impulses improperly controlled constitute a syndrome ("impulsivity," "dyscontrol," "aggressivity") which is of increasing interest to physicians.

## Structural Levels

Since the days of Hughlings Jackson, consideration of structural levels in the CNS has thrown light on the nature of normal and abnormal behavior. In understanding clinical violence, the lower levels of the peripheral reflex, spinal cord, and brain stem may be passed over.

*Limbic Level.* The limbic lobe, limbic brain, and rhinencephalon are interchangeable terms for the "old brain" that phylogenetically preceded the neocortex of homo sapiens. Man could feel before he could think and every infant is good at feeling before he grows up and has a chance to become good at thinking. The feeling limbic area serves as the margin between the brain stem with its automatic mechanisms and the cerebral cortex with its self-conscious, cognitive, and ruminative mechanisms.

Until recently little was known about the limbic structures — the cingulum, amygdala, commissures, fornix, hippocampus, thalamic and hypothalamic nuclei, portions of the temporal lobes, and other adjacent cell masses and interconnecting fibres. These deeply buried portions of the CNS are very sensitive to loss of oxygen at birth, and later to toxins, high fever, and many virus encephalitides, especially rabies. Here the pathologist looks for Negri bodies, and here electrical or chemical stimulation in animals causes "rabid" behavior or rage. This is the "emotional brain," the central area for the instincts. Here reside the raw emotions; only when they can be tempered by cerebral action can they become refined, subjective experiences. Only when constantly and efficiently controlled from above can they be kept consistent with civilized human behavior.

Pathologic change at the limbic level can produce episodic impulsivity and violence.

## Reports of Cases

*Case 1.* A 50-year-old machine-shop foreman entered the hospital following a fracas in which he was knocked unconscious by a younger and much larger man. For several months he had been verbally and physically assaulting the men who worked under him. Formerly a good-natured and friendly man, he had become surly, irascible, and belligerent. Since he was impossible to please and complained of headaches, his wife urged him to see a doctor, but he refused.

When the patient recovered consciousness in the hospital he would not cooperate with the examiner. Eventually he disclosed that his headaches started about a year ago and were increasing in frequency and severity. In recent weeks he had been having strange experiences. For no reason at all he would suddenly smell something foul and have a peculiar metallic taste in his mouth. Sometimes this would be followed by a whistling noise and he would feel himself getting enormously angry. Usually he could find somebody or something to blame. Once he smashed a fine calibrating instrument, several times he beat his children, and often he picked a fight with the men at work.

The neurological examination revealed choked discs, a quadrant defect in the visual fields and other indications of a brain tumor. At operation a large meningioma was removed from the right temporal region and the patient soon recovered his former affable personality.

*Comment:* It has long been known that tumors of the temporal lobe, particularly on the non-dominant side, may produce personality disorder for years, often with violent behavior. The diagnosis of organic brain pathology would be suspected from the history; the indications of brain tumor are usually found in the neurological examination. Confirmation and localization require specialized techniques.

*Case 2.* A 17-year-old youth was sent to a mental hospital for examination following an episode of wild rage in which he killed his mother with an ax. He had been known for his violent temper all his life and several times he had been in trouble with the authorities. In minor fights at school he would lose control of himself and would have to be pulled off his antagonist even after the latter had surrendered.

After the fourth school fight in which the victim had to have surgical attention, the patient was sent to a reformatory. There he was beaten up by an older boy and had to have stitches in his own scalp. On parole, he worked as a laborer but was fired from one job after another because of impudence to the foreman.

The father stated that his son had been a problem since birth. His delivery had been long and for a time the doctors could not get him to breathe. In infancy he had convulsions whenever he had a fever, and two or three times had had them without fever. He wet the bed until he was 11. At school he was slow in learning and his teachers said he was the worst-behaved child they had ever had. The father could not understand this, since his other four children had never been a problem at home or anywhere else. This boy was utterly rebellious and no form of discipline, lenient or severe, affected him.

The patient had been out late the night before his mother's death, and she was trying to get him out of bed at noontime. He raged at her, got up and pushed her out of his way. She was a large woman and when she defended herself he brushed against the corner of a bureau and scraped his arm. In a fury at the bit of blood, he picked up his younger brother's Boy Scout ax and hacked at his mother until the results were horrible beyond description. Later he denied any memory of what had happened but when pressed admitted he could dimly remember most of the details up to the time of the actual attack.

Psychiatric observation revealed that the patient had dull normal intelligence, no evidence of psychosis but a clear clinical picture of what was then called "psychopathic personality." The neurological examination, x-rays of the skull, and lumbar puncture were negative. An electroencephalogram, which at the time was a relatively new diagnostic procedure, threw light on the situation by disclosing abnormal brain waves. These occurred in spurts, unlocalized, and there were bursts of spike-and-slow-wave activity indicative of larval petit mal seizures.

Further study verified the diagnosis of psychomotor epilepsy. Diphenyl hydantoin improved the patient's behavior.

*Comment:* "Psychomotor epilepsy"<sup>3</sup> is a clinical term used to indicate episodic behavior disorder, largely involuntary and with impaired consciousness. Some observers use "temporal lobe epi-

lepsy" interchangeably. Usually, there is no indication of the cause, as in most cases of epilepsy, but it is assumed that the lesion is somewhere in the temporal lobe or elsewhere in the limbic area. There are perhaps 750,000 epileptic persons in the United States.<sup>4</sup> Fifteen percent of them, or more than 100,000, have psychomotor attacks.<sup>5</sup> Of those who do, perhaps 1 percent, or upward of 1,000, are prone to dangerously violent seizures and most of these epileptics are probably put into institutions.

\* \* \*

A third type of episodic violence associated with presumed pathology at the limbic level is only recently becoming recognized. It has been called the "dyscontrol syndrome" by Vernon Mark.<sup>6</sup>

*Case 3.* A 38-year-old married woman entered the hospital because of repeated attacks of wild, uncontrolled behavior. Without warning she would be assailed by intense feelings of either rage or sexual excitement. In rage she usually attacked her husband. In sexual excitement she sought a partner wherever she could find one. Often she exhausted one man after another with insatiable demands. The smallest amount of alcohol would be enough to inflame her sexual desire or set off a violent display of temper.

Prolonged psychotherapy and tranquilizing medication proved ineffective. An electroencephalogram was grossly abnormal. There were bursts of generalized seizure waves with a variable focus of activity in the fronto-temporal regions. Most of the abnormal activity was clearly subclinical, resulting in inattentiveness and confusion, but the build-up of voltage or more generalized spread of the focal abnormality presumably resulted in episodes of intolerable psychic tension which became channeled into rage or sexual excitement.

Diphenyl hydantoin changed this patient's behavior remarkably. She became quiet and amenable to reason.

*Comment:* The dyscontrol syndrome is characterized by four clinical features, not all of which appear in every case: (1) unprovoked brutality—beating wives, battering children, or assaulting friends or strangers; (2) pathological reaction to alcohol (dipsomania)—violent aggressiveness and belligerence on minimal amounts of liquor; (3) excessive and ill-controlled sexuality, often involving promiscuity, nymphomania, per-



version, and rape; (4) frequent auto accidents (often precipitated by rage at other drivers).

The syndrome is not a pathological entity, although a lesion or abnormality in the limbic lobe is hypothesized. It apparently overlaps the two entities previously mentioned—temporal lobe pathology and psychomotor epilepsy. All three demonstrate comparable clinical symptoms and signs, show similar EEG dysrhythmias, and respond to the same treatment (anti-convulsive medication and corrective or stereotaxic obliterative neurosurgical procedure).

The violence of limbic disease is characteristically episodic, largely unwilling, and associated with impaired consciousness and inappropriate responsiveness to the environment ("twilight state").

It is at the cortical level that man is uniquely man. The cerebral cortex controls the rational process, perception, evaluation, memory, symbolization, language, judgment, planning and wisdom. The instinctive urges report here and are translated into action and contact with the outside world, preserving unity between past, present and future. The executive functions of the personality reside here and arrange for decisions: acceptance, denial, compromise, postponement. Here sits the will and the source of all voluntary violence.

Violence may also be triggered by two kinds of disease in the cerebral cortex—organic disorder and idiopathic psychosis. The former is most commonly seen in states of intoxication.<sup>7</sup>

A large proportion of violent crimes are committed under the influence of alcohol, a drug notorious for its highly differential effect on individuals. It brings on belligerence, impulsivity, and temporary loss of normal inhibitory controls in perhaps 10 percent of heavy drinkers, and frank clinical violence in less than 1 percent (thus in only 50,000 or so of the eight million alcoholics in the United States).

*Case 4.* A brilliant nuclear physicist was voted out of his country club because of repeated episodes of grossly disorderly conduct. Normally a quiet and retiring man, he changed strikingly when he drank too much. He began by being playful and teasing with his wife, then became irritable and found a pretext for getting angry. If his wife and close friends did not succeed in

taking him home quickly he usually became combative. Just before he was referred to a psychiatrist he pushed an acquaintance at the club through a glass door and the man's face was badly cut.

Other toxic conditions of the cerebral cortex may produce violence in some individuals. Drugs such as barbiturates, marijuana, and narcotics of the morphine type that are widely abused are sedative and depressing in their reaction, but occasionally, like alcohol, produce a dangerous releasing reaction, with impairment of perception and judgment. The hallucinogens (LSD, psilocybin, glue vapor and others) are notorious for "bad trips" and associated bizarre and damaging consequences.

*Case 5.* A 20-year-old college girl went to a fraternity party where everyone smoked marijuana, took LSD, and sampled other undetermined drugs. Early the next morning she returned to her apartment on the third floor of a dormitory. Her roommate, noting her strange speech and behavior, tried to persuade her to go to the infirmary. Instead she suddenly went to a window and dived out to her death.

Cortical impairment can result from a wide variety of other pathological physicochemical conditions. Many of these produce so much physical incapacity that violence cannot be a problem except in the very early stages—for example, high fever, uremia, hepatic coma, hypoglycemia, diabetic acidosis, porphyria, hypoxia, and poisoning (heavy metals, venoms).

Structural cortical pathologic change—as, for example, in head injury—may produce abnormal behavior and violence in which transient mental confusion and strange antics sometimes dominate the clinical manifestations. Another example is senile dementia in which the cantankerous and sometimes extremely assaultive temperament is well recognized. Unexplained character change with violence may indicate brain tumor or cerebrovascular disease.

*Case 6.* A 49-year-old carpenter began to be extremely religious. He had never been a churchgoer but now he gave sermons to his wife, children, grandchildren—anyone who would listen. He felt that being a carpenter gave him Christ-like stature and that he had an important predes-

tioned role to play in the world. Were it not for his headaches and sudden impulsive rages, he would enter the clergy. In the last rage he broke all the windows in his house because he thought the air of Nature should circulate more freely.

The physical and neurological examinations were negative but x-ray films of the skull revealed suspicious areas of calcification in both frontal regions. Subsequent study and operation verified widespread glioma of the frontal lobes.

‘ ‘ ‘

In idiopathic psychotic entities that have no accepted organic cause (largely schizophrenias and manic-depressive psychoses), violence sometimes occurs, although not with the frequency that is supposed. Probably less than 50 percent of all psychotic persons are ever recognized as such, and of these less than 10 percent become violent. That still accounts for many thousands of violent episodes every year.

*Case 7.* A 32-year-old single woman was arrested for killing her newborn child. She was a very obese domestic, and no one ever knew she was pregnant. She had had two babies before, delivered them herself, suffocated them, and disposed of the bodies. This time she had been careless and her employer called the police. Psychiatric study revealed that the patient believed the babies were sent to test her courage. Destroying them proved she was fit to continue seeking the “servant of God” who would lead her to “salvation.”

‘ ‘ ‘

Where does illness leave off and badness begin? Some believe that every criminal should be considered mentally sick. These are no doubt the “tender minded” that William James spoke of—but tender to the point of being softheaded. What is criminal here and today may be heroic somewhere else and tomorrow. Psychiatry as the medical specialty for mental illness and mental health is not now, has never been, and scarcely ever could become the grand arbiter of all human behavior. Deliberate violence belongs in the realm of criminology, sociology, ethics, religion, diplomacy, and international relations.

Yet now and again one must seriously question whether an individual is insane or depraved. If the individual controls great power the results may devastate and shake the earth.

*Case 8.* A middle-aged housepainter became active in politics and by advocating a bold, revolutionary program at a propitious time and place he gathered millions of fanatic followers. Much of his success derived from ruthless and unscrupulous scapegoating of a specific minority group. He put to death six million men, women, and children of the minority group and nearly conquered the civilized world in warfare.

*Comment:* Violence caused by disease of the cerebral cortex is characterized either by confusion (in organic disorders) or irrationality (in idiopathic psychosis). In the former, volition is partial or absent, in the latter it is present but sick.

## The Differential Diagnosis

In evaluating the possible medical significance of a violent act, consider (1) its provocation, (2) appropriateness, (3) deliberateness, and (4) the characteristics of the attendant behavior.

1. Violent acts brought about by disease<sup>8</sup> are usually unprovoked or are precipitated by a stimulus that would be insufficient in a healthy person—for example, a student who sits in a campus tower and shoots at anyone in sight, a father who fractures the skull of his baby son because he will not stop crying, or a man who smashes furniture because the bartender will not serve him more liquor. Sometimes, however, a seemingly trivial provocation may actually be quite adequate in a normal person for a violent act. A man who has been harrassed by his boss all day comes home and finds his house door will not close properly. He finally slams it so hard he breaks a pane of glass. At the end of a hard day a wife flings a plate at a taunting, tipsy husband. Allowances must be made for exasperation, pique, and human frailty.

2. Bizarre acts label themselves as sick. A young man stabs a babysitter and her child 40 times. A vagrant strangles several women in their apartments, attacking their dead bodies sexually. The well-bred daughter of a professional man stabs a stranger with scissors in the ladies room of a theater. A young girl beats her friend into unconsciousness, pulls out her hair and stuffs it into her mouth. What is bizarre and inappropriate in one context, however, may be quite usual in another, as, for example, the maiming and grotesque disfiguring of enemy bodies in certain primitive tribal feuds.



3. In the common law, acts committed without conscious volition belong in the domain of the physician rather than the jurist. Violent acts that are committed in trance or twilight states, with complete absence of premeditation, conscious awareness, or later recall are suggestive of limbic disease and are clearly medical. Evidence of abnormal behavior or abnormal electroencephalogram are helpful in the diagnosis. Other violent acts occur in impassioned impulsiveness ("irresistible impulse"), with complete conscious awareness but with loss of control ("temporary insanity"). A wife surprises her husband in bed with her best friend and shoots. A young man catches his fiancée making love with someone else and goes berserk. In certain areas of the United States the wife would probably go free, but the young man would not. The physician rarely can contribute in cases of this kind. Acts committed while intoxicated, such as causing a fatal auto accident, are also legal problems and not medical.

4. The description of the attendant behavior in a violent act carries weight because it can be impartial, objective and diagnostically significant. Chronic dementia (loss of intellectual functions—memory, speech, reasoning, judgment) or pronounced personality deterioration indicate or-

ganic brain disease. Amnesia for the episode alone must be looked at askance, since it can easily be shammed. A dazed, befuddled, drunken or confused demeanor characterize cortical disease, often alcoholic or toxic. Irrationality, delusions, hallucinations or severe mood abnormalities (suicidal depression, maniacal elation, wild rage) mark violence as psychotic. Automatism or robot-like behavior with inappropriate responsiveness to the surrounding environment suggest limbic disease.

Most human violence is perpetrated by medically normal persons who show few or none of the above phenomena. They act impulsively emotional or deliberately malevolent.

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#### MISDIAGNOSIS IN CASES OF DEAFNESS

"While a failure to detect deafness is bad enough, far worse are the misdiagnoses that occur. In our experience at Michael Reese Hospital and Medical Center in Chicago, at least one-third of the parents of deaf children report early erroneous diagnoses. Some of these grow out of the very complex problem of differential diagnosis between mental retardation, brain damage, auditory agnosia, delayed speech, autism, childhood schizophrenia, and deafness. Often it's not a differential diagnosis of either/or, but it's a diagnosis of how much of each. Most hospitals for the retarded have entire units of patients for whom they are unable to make a diagnostic decision with regard to these confusing areas. I have personally found 15 deaf persons in institutions for the mentally retarded who were not retarded."

—McCAY VERNON, PH.D., Chicago

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# Snakebite or Frostbite: What Are We Doing?

## An Evaluation of Cryotherapy for Envenomation

HUGH A. FRANK, M.D., *La Mesa*

THE BITE OF A POISONOUS SNAKE can be a fatal injury. It creates instant terror in its victim and anxiety in his physician. The knowledge that his patient may lose part of his limb, or even die, spurs the physician on to use any treatment reported to be effective. It is not surprising, therefore, that cryotherapy,<sup>1</sup> a plausible recommendation, should achieve instant popularity in a medical community. This is especially so when it has been dramatically presented<sup>2</sup> by a positive proponent like Herbert Stahnke and widely publicized in the popular press. Its continuing popularity in the face of serious complications is due in part to the limited experience of any one physician with patients bitten by poisonous snakes. It is also due to the impossibility of critically evaluating the results of Dr. Stahnke's ligature-cryotherapy program in any clinical situation. One must consider on the one hand that a bad outcome in a snakebitten patient occurred in spite of the use of cryotherapy, or because cryotherapy was used incorrectly or too late, and on the other the possibility that the bad outcome might be because cryotherapy itself added to the damage caused by snake venom.

Since 1960 I have had occasion to repair and reconstruct a number of limbs which had first been bitten by poisonous snakes and then been treated by cryotherapy. My interest was aroused when I noted how similar the damage was to

that caused by cold immersion as I had observed it during World War II.

The difficulty in clinically evaluating cryotherapy (or any other therapy) arises from the nature of snakebite itself. The seriousness of such a bite depends upon the amount of venom injected, the toxicity of that particular venom, and the location at which the venom was deposited. In any given patient none of these significant variables can be known or even guessed at until the poison has done its ultimate damage. Even the location of the fang marks gives no exact indication of where the poison is—it may have been placed intravenously. A widely used clinical classification of the degree of envenomation<sup>3,4</sup> is based on the observed condition of the patient 12 hours after the bite. But by that time therapy of some kind has been given in almost every case. Therefore, the observed condition of the patient is usually the net effect of the snakebite and its treatment. If a treatment is used which not only is ineffective, but which by itself can produce similar injurious effects or which can actually enhance the injurious effects of the venom, the picture is even further confused.

Collected statistics for California<sup>4</sup> as well as elsewhere, indicate that mortality due to snakebite is rare, about one-half of one percent. Permanent damage or loss of portions of limbs as a result of snakebite is common when any significant envenomation has occurred.<sup>5</sup> It is imperative, therefore, to know whether we are doing harm or good to the bitten limb when we ad-

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minister cryotherapy. In my opinion this question can only be answered by looking to experimental studies including envenomation with and without cold immersion and to studies of the effect of cold immersion without envenomation. Fortunately many such studies have been made.

According to Stahnke<sup>1</sup> the rationale of the ligature-cryotherapy treatment is as follows. Rapid absorption and systemic distribution of the snake venom and of tissue breakdown toxins can be prevented, first by the placement of a constricting ligature around the limb between the bite and the body, and subsequently by rapidly reducing the temperature of the tissues around the bite. Local destruction of tissues by the enzymatic actions of the venom can also be prevented by lowering the tissue temperature. If, in addition, the body generally is kept warm and circulation is supported, natural detoxification processes can cope with the small quantities of venom which are slowly absorbed and can ultimately protect the patient from both general and local destruction. Lastly Stahnke asserts that immersion of a limb in ice water, even for several days, is not in itself harmful if the rest of the body is kept warm and circulation is supported.

No one seriously questions Stahnke's first assumption that rapid systemic absorption of toxic substances can be prevented by the ligature and cryotherapy or that local destruction of tissues by the venom can be slowed or stopped by cold. However, experimental observations do not support his contention that ultimate detoxification without loss of life or limb can occur during and as a result of cryotherapy. Nor do they support his contention that cold immersion *per se* is not harmful. Let us examine the evidence.

Keating's monograph summarizes the literature of many years with respect to cold injury of the limbs.<sup>6</sup> He points out that "prolonged exposure to water colder than 15° C produces a characteristic pattern of changes that include lasting damage to nerve and muscle." . . . "Six hours' exposure seems to have been required to produce fully developed cases of 'immersion foot'." . . . "In a few cases of immersion injury blood flow never returned to some areas, apparently because of thrombosis of arteries supplying them, and these ischemic areas often became gangrenous." . . . "There was some indication that arterial thrombosis and gangrene occurred

only when limbs had been exposed to trauma as well as cold."

If cold immersion alone can produce tissue destruction, what will it do when combined with the trauma of snake venom, itself capable of producing tissue destruction? Stahnke recommends<sup>1</sup> placing the bitten member directly in iced water (0°C) for the first four hours and then protecting the surface with a layer of plastic sheeting and continuing the immersion in iced water for at least 12 hours and often for four to six days of continuous treatment. Tissue destruction would be expected in some patients so treated even if they had never been bitten at all. One patient referred to me after cryotherapy for snakebite had had his forearm and hand immersed in ice water for ten days. Yet the loss of his fingers and of the function of his forearm was attributed by his physician to the snakebite.

Obviously prolonged cold immersion, with or without a tourniquet obstructing blood flow, and with or without snake envenomation, has its hazards. Is there any real evidence that it ameliorates the lethal or the local effects of snake venom?

Since in humans the quantity of venom injected, its toxicity, and its exact locus are always unknown, the effects of therapeutic measures can only be evaluated in animal experiments in which all three of these factors can be standardized. McCollough and Gennaro<sup>5</sup> in 1963 reviewed the experimental studies to that date and added new studies of their own, using radioisotope tagged pooled rattlesnake venom and radioisotope tagged polyvalent antivenin crotalidae in anesthetized dogs. Measured doses of standardized venom per kilogram of animal produced consistent and reproducible toxicity. They, and previous investigators<sup>7</sup> clearly demonstrated under controlled conditions the following facts:

- Local tissue necrosis produced by rattlesnake venom is not decreased by local cooling and in most instances is greater than in untreated animals.

- There was no evidence that local hypothermia (cryotherapy) was of value as definitive therapy, since all animals treated by local hypothermia alone died following injection of lethal amounts of venom.

- If administration of antiserum was delayed for as long as eight hours after injection of venom, some increase in survival was obtained by local hypothermia; however, if antiserum was administered within four hours after envenomation, no benefit of local hypothermia was apparent. What increase in survival there was, was obtained at the price of increased local tissue destruction.

- Using  $I^{131}$  labeled antivenom administered intravenously, it is possible to demonstrate 85 percent of the administered dose of antivenom in the envenomated leg within two hours' time. However, cooling prevents or considerably reduces the amounts of  $I^{131}$  labeled antivenom which collects at the site of envenomation.

"Without the knowledge of these experimental facts, but with the favorable publicity in news and sports publications," McCollough and Gennaro said, "the rationale of cryotherapy seemed logical, and many physicians" continue to use it. Clinical reports attesting its value continue to appear, but analysis of these reports is useless because the degree of envenomation is always unknown and cryotherapy is seldom used as the sole treatment. In light of the evidence that

cryotherapy's only real value is in delaying damage when definitive therapy cannot be secured for more than four and less than eight hours after envenomation, and that even this limited benefit can be obtained only at the price of increasing the ultimate damage at the envenomation site, it appears strongly recommended that the method ought to be used rarely if ever. Reliance should be placed mainly on anti-tetanus, antibiotic and antivenom therapy—recognizing the while the not inconsiderable hazards of the antivenom also.

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## FLAREUPS FROM X-RAY

Does the usual preparation of the colon for colonic x-ray possibly cause a flare-up of ulcerative colitis?

"It does. In the first place I don't think you should x-ray patients with severe acute ulcerative colitis or moderately severe ulcerative colitis. Frequently a preliminary film of the abdomen is all you need. If you need follow-up studies to exclude carcinoma, most of these patients are in a chronic state, so it's all right. But some of these patients do come in with severe diarrhea; we just put them on a liquid diet and give them the enema ourselves. The other problem is that many patients with mild and chronic ulcerative colitis have multiple fecal impactions in their colon because they've been taking all kinds of drugs to stop the diarrhea, and to x-ray these patients is a *tour de force*. You just have to be persistent—put them on liquid diets and multiple low enemas. I stay away from cathartics in preparing patients who have ulcerative colitis."

—RICHARD H. MARSHAK, M.D., New York City  
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 For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Recent Progress in Calcium Metabolism: Clinical Application

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*"Those who do not know the past are  
condemned to relive it."—Santayana*

IN THE LAST DECADE accurate calcium determinations, once found only in highly specialized research laboratories, have become generally available. As a result, the practicing physician is often confronted with minor deviations from normal which he must assess. Hyperparathyroidism, once thought rare, is recognized with increasing frequency. This technological advance has been accompanied by similar progress in scientific knowledge. Copp's<sup>1</sup> clarification of the factors responsible for the precise control of calcium homeostasis has added a new dimension to physiology and pathophysiology. DeLuca's<sup>2</sup> brilliant demonstration of chemical activation of vitamin D, and Avioli's<sup>3,4</sup> elucidation of the role of this process in health and disease, have added considerably to our understanding of disturbed calcium metabolism. Not surprisingly, clinicians have quickly sought therapeutic applications of

these discoveries. The time seems ripe to review this recent progress and to reexamine previous information in the light of new developments.

Since this review is primarily clinical in scope, many important basic scientific contributions—such as the role of cyclic adenosine monophosphate (AMP) in parathyroid hormone action—the clinical applications of which are not yet clear, are not included. By the same token, important clinical problems for which there is no clue to solution—for example, endocrine adenomatosis—are omitted. On the other hand, speculation and personal opinion on controversial clinical subjects, clearly indicated as such, are generously included.

## Calcium Homeostasis

The serum calcium level is one of nature's biologic constants. Normally, it varies little from species to species, with the seasons or time of day, and only slightly between the sexes. As early as 1907, Erdheim<sup>5</sup> described the calcioprotective law, stating that nature protects the serum calcium level at the expense of bone. Erdheim showed that in experimental rickets the already

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demineralized bone is compromised further by parathyroid overfunction. It is now clear that the parathyroid hyperplasia of rickets or osteomalacia is the natural consequence of hypocalcemia. A fall in serum calcium levels stimulates parathyroid secretion; conversely, hypercalcemia turns it off.<sup>6</sup> But this simple, readily demonstrable feedback mechanism by itself cannot explain the precise, minute-to-minute control of the serum calcium level. If one removes the parathyroid glands of a dog, it takes at least 150 minutes before the serum calcium level falls.<sup>7</sup> Clearly, the previously secreted parathyroid hormone is still acting several hours later. As a consequence, it follows that, if the parathyroid feedback were the only control of the serum calcium level, each fall would cause a prolonged and hypercalcemia rise. Conversely, each rise above normal turns off the gland, but cannot promptly lower the calcium level to normal.

Copp's<sup>8</sup> discovery of calcitonin, which lowers serum calcium levels promptly, slightly and briefly in response to hypercalcemia, provides the missing link necessary to explain the precise, rapid control of the serum calcium level. Parathyroid hormone is the coarse adjustment; calcitonin is the fine adjustment. Parathyroid hormone acts by mobilizing calcium from the large bone reservoirs; calcitonin inhibits this process. What this hormone is doing in the ultimobranchial glands of elasmobranchs,<sup>9</sup> which have cartilaginous rather than osseous skeletons, is unknown. Its presence in this species suggests other thus far undefined actions.

In mammals, the antiosteolytic action of calcitonin causes serum calcium and phosphate levels both to fall. The precise balance of parathyroid versus calcitonin maintains the normal serum calcium level.

## Role of the Sex Hormones

While parathyroid hormone and calcitonin are the only hormones known to have a feedback relationship to serum calcium levels, they are not the only hormones to control calcium equilibrium between gut, blood, bone, urine and feces. It has long been known that estrogens and androgens produce positive calcium balance.<sup>10</sup> Kinetic analysis shows that their mechanism of action on bone is not, as originally thought, anabolic, but anti-catabolic.<sup>11-18</sup> During their administration, calcium balance becomes positive, but, surpris-

ingly, the rate of bone accretion does not rise; it actually falls. Therefore, the gain in calcium cannot be the result of increased bone formation but can only be the consequence of decreased bone breakdown. Their action is therefore qualitatively similar to that of calcitonin.

This mechanism, previously shown by indirect means, has recently been confirmed directly by Riggs, Jowsey and their co-workers,<sup>19</sup> using quantitative microradiography of iliac crest biopsy specimens in human postmenopausal osteoporosis. This important action has also been implicated indirectly in normal women and in patients with postmenopausal osteoporosis, breast cancer and acromegaly. Like calcitonin, estrogens and androgens lower serum calcium and phosphate levels.<sup>20-24</sup> Conversely, the serum phosphate level is raised in osteoporosis, breast cancer and in acromegaly.<sup>21,25,26</sup> It is likely that the slight lowering of normal serum calcium levels of women between puberty and the menopause also reflects the braking action of endogenous estrogens on osteolysis.<sup>27-29</sup>

## Importance of Normocalcemia

The elaborate protection of the serum calcium level throughout the animal kingdom emphasizes the importance of the physiologically active calcium ion concentration. Until now this fraction has not been readily measurable. The advent of calcium electrodes may alter this situation. It should be borne in mind, however, that the ionic moiety is in equilibrium with the protein-bound fraction so that normally about half of the total serum calcium is in the free form. One cannot simply insert a calcium electrode in a random serum specimen at room temperature and determine the biologically significant calcium ion concentration. Factors known to influence the equilibrium between free and protein-bound calcium (temperature, pH, ionic strength, and quantity and quality of serum proteins)<sup>30</sup> require careful handling of serum or plasma specimens for meaningful calcium electrode measurements.

Clinically, the importance of the serum calcium level lies in its effect on neuromuscular irritability and central nervous system activity. A fall of 15 percent or more produces neuromuscular hyperirritability manifested as tetanic spasms of skeletal muscle, and seriously impairs mental processes. A similar rise inhibits smooth muscle contractility, especially in the gastrointestinal



tract, causing anorexia, nausea, vomiting, constipation, ileus and abdominal pain. Moderate hyperealcemia inhibits the action of antidiuretic hormone on the distal renal tubule leading to hyposthenuria, nocturia, polyuria, thirst and dehydration.<sup>31,32</sup> Greater rises may precipitate uremia and central nervous system symptoms such as lethargy, somnolence, psychosis and coma. The nonspecificity of the individual symptoms of mild hypocalcemia and hypercalcemia may delay recognition of the underlying chemical abnormality until the typical symptom complex is fully developed, unless serendipity leads to a screening panel of blood chemistry.<sup>33,34</sup>

### *Adrenocorticosteroids*

Like the gonadal steroids, adrenocorticosteroids have powerful effects on calcium homeostasis. It has long been recognized that Cushing's syndrome is characterized by a specific type of bone depletion. The osteoporosis of Cushing's syndrome, endogenous or exogenous, differs from that of postmenopausal osteoporosis in distribution, kinetics, and roentgen appearance of the involved bone. Unlike postmenopausal osteoporosis, the type induced by corticoid overdose often leads to rib fractures.<sup>35</sup> Like postmenopausal osteoporosis, Cushing's disease often involves the vertebrae, but their roentgen appearance is quite different; eburnation, or marginal thickening of the superior and inferior vertebral plates, characterizes Cushing's syndrome,<sup>36,37</sup> but not postmenopausal osteoporosis.

The most perplexing feature of the action of cortisone on bone is that an agent which causes severe skeletal breakdown, the mechanism which most commonly causes hypercalcemia, is itself extremely effective in correcting many kinds of hypercalcemia. This latter action has been well documented in the hyperosteolytic hypercalcemias of malignant disease and thyrotoxicosis as well as in those due to excessive intestinal absorption of calcium—for example, vitamin D intoxication and sarcoidosis.

It has recently been demonstrated that glucocorticoids inhibit the conversion of vitamin D to its biologically active forms.<sup>38</sup> This inhibition may contribute to the antihypercalcemic effects of these agents, but cannot by itself explain cortisone's antihypercalcemic efficacy. Cortisone also lowers normal serum calcium levels in man<sup>21</sup> and in rats.<sup>39</sup> This effect is similar to the action

of calcitonin or of estrogens and androgens. In organ culture, cortisone prevents the osteolytic effects of vitamin A or of antiserum.<sup>40</sup>

These paradoxical effects, osteolytic on the one hand and antihypercalcemic on the other, can be integrated into a unified but heretical working hypothesis. It is tempting to speculate that the primary action of cortisone on bone is *anabolic* as shown in organ culture, in the effect on the normal serum calcium level, in hypercalcemia, in the roentgen appearance of the vertebral plates, and in their initial stimulation of skeletal dynamics. It has been shown experimentally both in man and in rats that in the absence of the parathyroids, corticoids conserve rather than waste calcium and phosphate.<sup>41,42</sup> It therefore seems possible that the calcium-wasting effect of corticoids may be mediated by the parathyroids in response to the fall in serum calcium these agents produce. Direct measurements of parathyroid hormone during corticoid administration have been made too rarely for direct assessment of this hypothesis.

### *Thyroid*

Like the corticosteroids, thyroid hormones in excess are potent catabolic agents. This action is well shown by the hypercalcemia and hypercalciuria of thyrotoxicosis. Histologically, the bone shows very severe osteoporosis, even osteitis fibrosa.<sup>43</sup> Clinically, this osteoporosis is not apt to produce skeletal symptoms except in postmenopausal women.<sup>44</sup> Here, however, the distribution of the osteoporosis, involving ribs and skull, which are not so often visibly involved in postmenopausal osteoporosis, may suggest the diagnosis. In addition, correction of thyrotoxicosis alone may stop the fractures. In physiologic amounts, thyroid is essential both for maturation and for normal transfer of calcium from the serum to bone. Failure of this transfer in myxedema may cause hypercalcemia.<sup>45</sup> Thus, both hypo- and hyperthyroidism can cause hypercalcemia, though by different mechanisms.

### *Growth Hormone*

The actions of the pituitary growth hormone on calcium metabolism are complicated. Like thyroid, growth hormone is essential for normal skeletal growth and may be useful in augmenting this process both in growth deficiency<sup>46</sup> and normal states.<sup>47</sup> In excess, however, growth hormone

causes hypercalciuria,<sup>48</sup> probably for the most part because of its effect upon the renal tubule, though excessive osteolysis can also be inferred.<sup>12</sup>

### *Vitamin D*

The last endogenous humoral agent in this array of calcium-active agents is vitamin D. In physiologic amounts—500 International Units (IU) a day—vitamin D acts on the intestinal tract to promote calcium absorption. In pharmacologic doses—for example, 50,000 to 150,000 IU per day—it directly lyses bone to release calcium. Pharmacologic doses also act on the renal tubules to lower tubular reabsorption of calcium so that hypercalciuria may occur even in the presence of hypocalcemia.<sup>49,50</sup> Provitamin D<sub>3</sub>, or 7-dehydrocholesterol,<sup>51</sup> is made in the skin and metabolized, under the influence of ultraviolet irradiation, to cholecalciferol (vitamin D<sub>3</sub>). In this form, vitamin D<sub>3</sub> is inert until activated in the liver and intestine.<sup>52</sup> The best established active metabolic product, 25-hydroxycholecalciferol (25-OH-D<sub>3</sub>), directly and rapidly lyses bone in organ culture.<sup>53</sup> As Avioli and his group have shown, activation of vitamin D<sub>3</sub> to 25-OH-D<sub>3</sub> is deficient in steatorrheas, uremia, and after corticoid administration.<sup>38</sup> The intestinal malabsorption of calcium, which characterizes the steatorrheas and uremia, can be explained by failure of this mechanism. The secondary hyperparathyroidism of osteomalacia and of uremia follow naturally. In contrast, the pathogenesis of the peculiar type of osteoporosis—*not* osteomalacia—which characterizes Cushing's syndrome remains unexplained.

### *Disorders of Calcium Metabolism*

Because *hypercalcemia* can cause serious, even fatal, acute damage or may insidiously compromise renal function, it is of great clinical importance. Interest in hypercalcemia has escalated, probably because of better availability of accurate calcium determinations, as well as enthusiasm for new and resurrected methods of treatment. Severe hypercalcemia is a medical emergency and requires rapid recognition and control. Chronic hypercalcemia too is damaging. In both types, correction of the underlying cause is the treatment of choice, but in the acute form emergency measures are life-saving. If the serum calcium level is moderately elevated, say to no more than 12.5 mg per 100 ml, hydration alone is corrective in most

hypercalcemias other than hyperparathyroidism.<sup>54</sup> Conversely, mild hypercalcemia may be exacerbated by dehydration, sometimes to severe or even fatal levels. Perhaps dehydration is the reason why thiazides exacerbate the hypercalcemias of hyperparathyroidism or of malignancy.<sup>55-57</sup> In all types of hypercalcemia, hydration is the first line of defense. Sodium-containing solutions are particularly effective.<sup>58</sup> As was pointed out by Walser, increasing the serum sodium level, where feasible, is in itself a powerful way to stimulate calcium excretion.<sup>59</sup> In most hypercalcemias other than hyperparathyroidism, pharmacologic doses of glucocorticoids are also highly effective, correcting hypercalcemia in most cases of vitamin D intoxication, sarcoidosis and thyrotoxicosis, and in about half those of malignant disease. Corticoids are less effective in hyperparathyroidism, perhaps in 10 percent of the type due to parathyroid adenoma<sup>60</sup> and in about 20 percent of cases where parathyroid hormone is formed ectopically by a "non-endocrine" cancer.<sup>61</sup> Other emergency measures such as intravenous administration of sodium sulphate<sup>62</sup> and hemodialysis<sup>63</sup> are of transient but sometimes life-saving value.

While phosphate administration, either oral or intravenous, is highly effective in lowering serum calcium levels, it may be extremely dangerous because of ectopic calcification, except in the presence of phosphate depletion. On the other hand, this form of treatment is probably safe and may be the treatment of choice where hypercalcemia is accompanied by severe hypophosphatemia following a successful renal transplant, in the diuresis following renal shutdown,<sup>64</sup> or in some cases of hyperparathyroidism.<sup>65,66</sup> Calcitonin has been reported transiently effective in correcting hypercalcemia in a few cases of various causes.<sup>67-70</sup> Because of its brevity of action, it must be injected frequently in a gelatine menstruum. Its use is still investigational and should be restricted to those cases in which the cause cannot be corrected and the hypercalcemia controlled by standard procedures such as hydration and corticoid therapy.

### *Drastic Treatment of Hypercalcemia*

In most cases, it is good medicine to ascertain the cause of hypercalcemia and correct it, especially in primary hyperparathyroidism, milk-alkali syndrome, sarcoidosis, hypervitaminosis D, thyrotoxicosis, post-uremia phosphate depletion, or controllable malignant diseases. Where this is



not feasible, or where the underlying cause cannot be readily corrected, as in widespread malignant disease, and where hydration and corticoids alone do not control hypercalcemia, other measures must be considered. The use of cytotoxic anti-tumor agents to treat hypercalcemia, originally shown by Myers for diazo-oxo-norleucine (DON)<sup>71</sup> and then for methotrexate,<sup>72</sup> has recently been extended to actinomycin<sup>73</sup> and to mithramycin.<sup>74,75</sup>

These agents need not be given in toxic doses, nor do they affect hypercalcemia by controlling tumor growth. For example, mithramycin also lowers the elevated serum calcium level of hyperparathyroidism.<sup>75</sup> Moderate doses of cytotoxic agents—for example, 500 mg of 5-fluorouracil intravenously—are as effective and less toxic.<sup>76</sup> It is likely that these agents act by inhibiting osteocytic osteolysis, one of the mechanisms which supports the normal serum calcium level. Before taking counsel of despair and using desperate measures, the physician should remember that all the body's homeostatic mechanisms favor the patient and that most hypercalcemias other than hyperparathyroidism respond to hydration and corticoids.

### *"Tertiary" Hyperparathyroidism*

It is not surprising that the hypercalcemia which sometimes follows successful renal transplantation has been equated with hyperparathyroidism. Parathyroid hyperplasia and hyperfunction are features of severe renal insufficiency,<sup>77,78</sup> and the combination of hypercalcemia and hypophosphatemia strongly suggests hyperparathyroidism. The occasional occurrence of parathyroid adenomas in patients with previous causes for secondary hyperparathyroidism has led to the attractive concept of autonomous or "tertiary" hyperparathyroidism. This term, independently coined by Walter St. Goar in 1963,<sup>79</sup> has so captured the imagination that the German author, Kuhlencordt,<sup>80</sup> has recently claimed priority for his compatriot Bock, who used this term in 1957.<sup>81</sup> Regardless of who published first, "tertiary" hyperparathyroidism is probably a myth. It is by no means certain that the incidence of parathyroid adenomas in renal insufficiency or in steatorrhea<sup>82-86</sup> is more frequent than can be accounted for by coincidence. In most of the hypercalcemias which follow renal transplantation or renal shutdown, parathyroid hormone levels are low or

absent.<sup>87,88</sup> In well controlled series the hypercalcemia following renal transplantation is infrequent and of multiple causes.<sup>87-89</sup> We have seen post-transplant hypercalcemia caused by the use of calcium salts as antacids, which are commonly used in these patients to counteract the gastric effects of corticoids that are being taken by patients as part of their immunosuppressive therapy. Some hypercalcemias are due to mobilization of ectopic calcium phosphate deposits, probably as a consequence of postcorrectional hypophosphatemia.<sup>61</sup> The hypophosphatemia following successful renal transplantation probably results from a combination of bone healing, increased phosphate clearance, lowering of tubular reabsorption of phosphate by corticoids<sup>21</sup> and use of aluminum antacids which bind dietary phosphate.<sup>90</sup> The few parathyroid adenomas found in uremic patients are probably either coincidental or the cause, rather than the result, of uremia. It is a fundamental error to equate hypercalcemia with hyperparathyroidism.

### *Medullary Carcinoma of the Thyroid*

Medullary carcinoma is a tumor of the calcitonin-producing parafollicular cells, which in submammalian species are found in the ultimobranchial body. Calcitonin overproduction is now well established as a feature of medullary carcinoma of the thyroid.<sup>91-93</sup> Earlier suggestions that excess calcitonin might cause pseudohypoparathyroidism,<sup>94,95</sup> a thesis inconsistent with the hyperphosphatemia of pseudohypoparathyroidism, have now been disproved.<sup>96</sup> Despite secretion of large quantities of calcitonin, medullary carcinoma rarely causes hypocalcemia, probably because of the efficiency of homeostatic defenses. One of these responses, parathyroid stimulation, may account for part of Sipple's triad: medullary carcinoma of the thyroid, hyperparathyroidism and pheochromocytoma.<sup>97</sup> Patients with medullary carcinoma as part of this triad are noted to have a particular facies.<sup>98,99</sup> Some of the other clinical manifestations of medullary carcinoma, such as diarrhea, may result from secretion of prostaglandins.<sup>100</sup> Ectopic secretion of calcitonin by nonendocrine tumors, first suggested by Prader,<sup>101</sup> has now been established by Milhaud et al<sup>102</sup> in a case of bronchial carcinoid. Whether this is truly an example of ectopic production or will characterize such tumors remains to be seen.

## Hypoparathyroidism

This condition occurs as an inadvertent consequence of thyroidectomy, for unknown cause (idiopathic), or in association with brachydactyly, short stature, round face and resistance to parathyroid hormone (pseudohypoparathyroidism). Renal resistance to parathyroid hormone in pseudohypoparathyroidism has been traced to absence of renal adenyl cyclase.<sup>103</sup> Serum parathyroid hormone levels are nil in the first two forms and greatly elevated in pseudohypoparathyroidism. Roentgen evidence of elevated parathyroid hormone levels may be found as subperiosteal resorption of the phalangeal cortex.<sup>104,105</sup> Why this resorption fails to correct hypocalcemia is unexplained. In pseudohypoparathyroidism, elevated serum parathyroid hormone (PTH) levels quickly revert to normal when vitamin D restores normocalcemia.

## Treatment of Hypoparathyroidism

Since hypocalcemia and hyperphosphatemia both must be corrected to control tetany and to prevent metastatic calcification, classical therapy used to include calcium-mobilizing sterols (vitamin D<sub>2</sub>, vitamin D<sub>3</sub>, and dihydrotachysterol), supplemental calcium, a low phosphate diet and oral aluminum salts to bind dietary phosphates. It has subsequently become clear that adequate doses of vitamin D suffice to restore normocalcemia without added calcium supplements. In addition, patients whose hypoparathyroidism is well controlled by vitamin D can excrete oral phosphate loads normally, so that a low phosphate diet is not necessary.<sup>106</sup> Thus, in most patients, oral calcium salts and low phosphate diets serve only to complicate the therapeutic regimen and favor iatrogenic hypercalcemia.

In the vast majority of cases of hypoparathyroidism, vitamin D alone provides adequate therapy. It raises the serum calcium and lowers the serum phosphate level to normal. Adequacy of treatment is judged entirely by the blood chemical levels. Observing the urinary calcium excretion (Sulkowitch test) as a way to evaluate adequacy of treatment is misleading since vitamin D produces hypercalciuria before the serum calcium level rises to normal.<sup>49-51</sup> It must be borne in mind that vitamin D takes six to twelve weeks to obtain its full effect; that about 95 percent of patients with hypoparathyroidism achieve normal serum

calcium and phosphate levels when treated with doses of 50,000 to 150,000 units a day; and that the actions of the agent may persist six to twelve months after administration has been discontinued. Failures of therapy are most commonly due to use of a poor preparation,<sup>107</sup> since vitamin D is a labile material with a rather short shelf life.\* Vitamin D resistance in hypoparathyroidism is rare; when encountered, dihydrotachysterol is reported to be effective.<sup>108</sup> Some preparations, formerly used widely and with rather poor results, have been shown to contain no dihydrotachysterol.<sup>109</sup> Fear that the use of large doses of vitamin D in pregnant women with hypoparathyroidism may result in fetal cardiovascular malformation<sup>110</sup> happily has not been borne out in practice.<sup>111</sup>

## Pitfalls in the Diagnosis Of Hypoparathyroidism

Because of the long action of vitamin D, it may be very difficult to ascertain whether the original diagnosis of hypoparathyroidism in the vitamin D-treated patient was in error. Following any surgical procedure under general anesthesia, the serum calcium level drops, sometimes as low as 7.8 mg per 100 ml and the serum phosphate level rises.<sup>112-114</sup> If the operation was a thyroidectomy and the patient has Chvostek and Trousseau signs from anxiety or hypocalcemia, these phenomena may lead to an incorrect diagnosis of hypoparathyroidism. The nonspecific hypocalcemia following general anesthesia subsides in a few days, while that of hypoparathyroidism persists or becomes worse. Early vitamin D treatment is both irrational and misleading since the onset of action is slow and the long action requires months of withdrawal to ascertain whether the blood calcium level is maintained by endogenous parathyroid hormone. For these reasons it is advisable to treat postoperative hypocalcemia with short-acting intravenous and oral calcium preparations rather than vitamin D and to defer diagnosis for

\*In reviewing this manuscript, Dr. John Eager Howard called my attention to the fact, unknown to me, that vitamin D, while unstable in crystalline form is good for at least 50 years in oil or propylene glycol. Therefore, our unhappy experience with generic vitamin D is probably due to poor preparations rather than instability. Our troubles disappeared in 1961 when The Upjohn Company generously supplied us with vitamin D (Calciferol) Geltaabs®, 50,000 I.U. (1.25 mg.). Of 150 patients with hypoparathyroidism, all but four were rendered normocalcemic, or nearly so, by doses of 50,000 to 150,000 I.U. daily. Three years ago, The Upjohn Company temporarily discontinued this preparation. Patients who had been well controlled were now hypocalcemic or hypercalcemic while receiving the same dose formulated by other manufacturers. When Upjohn's vitamin D was again used, good control was again achieved. This convinced us of the importance of using a well calibrated standard preparation rather than prescribing generic vitamin D. It is likely that alleged failures of vitamin D in renal osteodystrophy, osteomalacia and hypoparathyroidism result from the use of poor preparations.



at least a week. In the vitamin D-treated patient, two techniques may facilitate demonstration of normal parathyroid function. One of these is the response to corticoids, which rapidly precipitate tetanic levels of hypocalcemia in patients with hypoparathyroidism.<sup>115,116</sup> The other is the less generally available parathyroid hormone assay; measurable parathyroid hormone in the serum serves to exclude hypoparathyroidism. Otherwise vitamin D may have to be withdrawn for a year or more before the serum calcium levels fall. It is a fundamental mistake to equate tetany with hypocalcemia, or hypocalcemia with hypoparathyroidism.

### *Hyperparathyroidism*

**Diagnosis.** Hyperparathyroidism, once rare, is now recognized relatively often because of the general availability of accurate calcium determinations. It must be reemphasized that hypercalcemia is not to be equated with hyperparathyroidism, but that hypercalcemia is virtually essential for the diagnosis. Normocalcemic hyperparathyroidism is rare; parathyroid exploration in normocalcemic subjects leads to many "negative operations." In proved hyperparathyroidism, hypercalcemia may be masked temporarily by a high phosphate intake,<sup>65,66</sup> by concomitant intestinal malabsorption,<sup>86</sup> by acute pancreatitis,<sup>117</sup> or by an infarct of a parathyroid adenoma.<sup>118</sup> Of these, the most common is a high phosphate intake, for some patients with hyperparathyroidism, like Curt Richter's parathyroid extract-treated rats,<sup>119,120</sup> have an increased appetite for phosphate. A low phosphate diet rapidly restores hypercalcemia if it has been obscured by a previous high phosphate intake.<sup>120-122</sup>

Recognition of those patients whose hypercalcemia is due to hyperparathyroidism can be accomplished in numerous ways, the least desirable of which is surgical "exploration." Hypophosphatemia, while helpful when present, occurs in less than half the cases.<sup>120,123</sup> Exclusion of other causes of hypercalcemia is inadequate, since 15 percent of patients with proved hyperparathyroidism simultaneously harbor additional diseases known to cause hypercalcemia.<sup>60</sup> In my experience, the best available diagnostic combination is that of hypercalcemia plus hyperphosphaturia (increased phosphate clearance or low tubular reabsorption of phosphate), in the absence of the few other conditions known to cause this combination (sarcoi-

dosis, myeloma, or vitamin D overdose).<sup>124-126</sup> Since hypercalcemia of other causes turns off the parathyroid, the combination of measurable serum parathyroid hormone levels and hypercalcemia is diagnostic of hyperparathyroidism. This constellation occurs both in primary hyperparathyroidism (parathyroid adenoma or hyperplasia) and in the syndrome where hyperparathyroidism arises ectopically from a "non-endocrine" cancer. Separation of parathyroid from ectopic causes of hyperparathyroidism may range from easy to impossible. In some cases, hypercalcemia may be the first manifestation of the underlying tumor. Other evidences of malignant disease, such as anemia, an elevated alkaline phosphatase level in the absence of roentgenologically visible subperiosteal resorption of the phalangeal cortex, response of hypercalcemia to corticoids, and serum chloride levels below 102 mEq per liter, should make one think of the ectopic syndrome.<sup>61</sup>

**To Treat or not to Treat.** The most difficult question to answer with the mild—often asymptomatic—kind of hyperparathyroidism seen nowadays is whether operation is really necessary. The severe hyperparathyroidism recognized from 1930-1950 often went on to uremia and hypertension despite removal of the causative parathyroid tumor.<sup>127,128</sup> The prognosis of milder hyperparathyroidism is not yet known.<sup>123</sup> Operation in borderline cases is often unproductive.<sup>129</sup> Since hypercalcemia insidiously damages the kidney and can become acutely life-threatening on dehydration or immobilization, clear-cut hyperparathyroidism should probably be corrected surgically in almost all cases. Where the condition is mild, asymptomatic and associated with other major disease in the elderly, one may consider non-surgical treatment by hydration, phosphate administration and the use of anti-osteolytic steroids.<sup>130</sup> This is probably an uncommon situation and the treatment appropriate in only a small proportion of carefully considered cases where the patient can be followed closely and frequently.

### *Renal Osteodystrophy*

The skeletal complications of uremia are the summation of the consequences of three processes: (1) *calcium malabsorption*, due to failure of activation of vitamin D leading to hypocalcemia and to (2) *secondary hyperparathyroidism*, as well as (3) *hyperphosphatemia* due to impaired

filtration of phosphate, causing abnormal deposits of calcium phosphate in bone (osteosclerosis) and soft tissues. Therefore, osteomalacia, osteitis fibrosa and osteosclerosis may co-exist in varying combinations.<sup>131-135</sup> Since the fundamental defects are calcium malabsorption<sup>136,137</sup> and hyperphosphatemia, pharmacologic doses of vitamin D or dihydrotachysterol, together with low phosphate diets and aluminum hydroxide, can and do reverse the process.

Before the advent of hemodialysis and renal transplantation, renal osteodystrophy was a terminal event in uremia, indicating a very short life expectancy. Nonetheless, when carefully treated with adequate doses of vitamin D or dihydrotachysterol (along with measures to lower the serum phosphate level), osteodystrophy was regularly reversible.<sup>76,131,138</sup> Hemodialysis and renal transplantation have altered the picture. If chronic hemodialysis is carried out with calcium concentrations of less than 6 mg per 100 ml of bath fluid, secondary hyperparathyroidism may be seriously aggravated; with higher concentrations, ectopic calcification may be precipitated.<sup>139-142</sup> The success of dialysis and renal transplantation has prolonged life so that, in many cases, renal osteodystrophy and ectopic calcification have come to dominate the clinical picture.

As discussed above (under the heading *Hypercalcemia*) there has been a recent tendency to overemphasize the value of therapeutic or even prophylactic parathyroidectomy. This operation of course necessitates replacement therapy with pharmacologic doses of vitamin D—which, in most cases, is successful without parathyroidectomy. Our experience, like that of others, is that the parathyroids are not autonomous in uremia, that hyperparathyroidism resolves after successful renal transplantation<sup>87,88,112-144</sup> and that post-transplant hypercalcemia is infrequent, not often associated with increased serum parathyroid hormone levels, and usually correctible by innocuous treatment. In the opinion of this reviewer, parathyroidectomy should be considered only after an adequate trial of vitamin D or in the event that the patient has both renal insufficiency and a parathyroid adenoma (coincidental primary, or so-called tertiary, hyperparathyroidism).

One possible reason for failure of vitamin D therapy is the lability of this sterol, leading to use in some cases of preparations with little or no

pharmacologic activity.\* This phenomenon is well known to physicians experienced in the treatment of hypoparathyroidism and is easily avoided by using a good preparation.

Kaye et al reported that dihydrotachysterol uniformly arrested hyperparathyroid bone disease in patients undergoing hemodialysis<sup>115</sup> and seriously questioned the desirability of parathyroidectomy in patients undergoing chronic dialysis. Dihydrotachysterol may be more easily controlled than vitamin D in patients with renal insufficiency because of its more rapid effect and shorter period of action. The danger of hypercalcemia from overdose of vitamin D or dihydrotachysterol is real, and in uremic patients can be especially hazardous because of the deleterious effects of hypercalcemia on renal function. Frequent monitoring of serum calcium levels is essential.

The renal insufficiency which follows prolonged and severe hypercalcemia is often associated with special forms of metastatic calcification. Since filtration of phosphate is impaired, a rise of serum phosphate levels occurs in all forms of severe uremia.<sup>146</sup> In the presence of hypercalcemia, a very high (Ca x P) product occurs, leading to calcium phosphate deposition in vital organs.<sup>147</sup> Rapid correction of the acidosis of this form of uremia favors further precipitation of calcium phosphate, especially in the pulmonary alveoli, producing a clinical picture similar to that of pulmonary edema. This complication is usually fatal; it is more easily prevented than treated, especially by avoiding a rapid rise of arterial pH and by correcting hyperphosphatemia.

## Osteoporosis

*Heterogeneity of osteoporosis.* Evaluation of medical literature on osteoporosis is extremely difficult because of confusion about types of patients treated, criteria for diagnosis, the type of osteoporosis present—if any—and difficulties in obtaining criteria for efficacy of treatment. It is important to recognize that there are three common heterogeneous types of osteoporosis with different pathophysiologic features and different clinical and roentgen appearances, for which different kinds of treatment may be indicated.

1. The *osteoporosis of disuse* can be localized or generalized, depending on the area of the body immobilized. While kinetic studies show an increase in the bone accretion rate,<sup>15</sup> suggesting that

\*See footnote on page 33.



accelerated osteolysis is the most important feature, it is also reasonable to believe that immobilization inhibits osteoblastic activity. With the converse — exercise — there is acceleration of bone accretion and bone density.<sup>148,149</sup> With immobilization the serum alkaline phosphatase level, the indicator of osteoblastic activity, falls.<sup>150</sup> An important feature of the osteoporosis of immobilization is that it often aggravates preexisting osteoporosis of other causes. Whenever possible, cessation of immobilization, or at least its reduction as much as feasible, is indicated.

2. By far the most common type of osteoporosis is the *post-menopausal* variety. The reason to implicate the menopause rather than old age<sup>151</sup> is based on its great frequency in women and relative rarity in men, and the fact that it can rarely be recognized less than ten years after a spontaneous menopause, or three years after oöphorectomy.<sup>76</sup> In addition, congenital absence of ovaries (gonadal dysgenesis) is almost universally accompanied by osteoporosis except in the variety where the interstitial cells secrete testosterone,<sup>152</sup> where osteoporosis is notably absent.<sup>153</sup>

3. The third large group where the etiologic delineation of osteoporosis is clear is that *due to excess glucocorticoids*. Previous arguments as to whether the action is catabolic or anti-anabolic<sup>154</sup> can now be settled by evidences that both processes occur at different times. In the first few weeks of administration of large doses of corticoids, bone accretion is greatly increased at the very time that calcium balance is strongly negative.<sup>14</sup> Later, or in spontaneous Cushing's disease, the bone accretion rate is low.<sup>148</sup> As suggested above, it is possible that the early catabolic effect may be mediated by the parathyroid, although it must be admitted that the bone lesion does not resemble that of hyperparathyroidism. Perhaps corticoids modify this appearance. The low serum phosphate levels and low tubular reabsorption of phosphate produced by corticoids<sup>21,155,156</sup> are consistent with parathyroid overfunction.

*Differential Diagnosis.* In addition to the three common types of osteoporosis, a disproportionate number of metabolic studies have been reported on the relatively rare idiopathic variety. Unfortunately, clinical investigation of this disorder has often been extrapolated to the therapy of other types of osteoporosis. It seems, also, that much osteoporosis exists only in the eye of the beholder. In our Bone & Stone Clinic, it is common to see

patients referred for treatment of osteoporosis in whom the diagnosis turns out to be carcinomatosis, myeloma, juvenile epiphysitis, vertebral osteophytosis, osteogenesis imperfecta, osteomalacia, or no demonstrable bone disease at all. In the latter, roentgen evidence for osteoporosis is often artifactual. The most common artifacts are increased radiolucency due to excess kilovoltage or milliamperage, and the false appearance of biconcave vertebrae produced by an improper positioning of the roentgen tube. A common clinical cause for error is misinterpretation of a transient backache (who hasn't had one?). The backache of osteoporosis is usually long-standing, non-radiating, non-tender (except during acute fracture) and situated in the lumbar or lower thoracic vertebra.

*Criteria for Diagnosis.* In reviewing reports on treatment of osteoporosis, it is often difficult to ascertain whether the patients did indeed have this condition. In practice also, to avoid treatment of a condition which is not there, it is desirable to have rigorous, objective criteria. These will necessarily be evidences of advanced osteoporosis, since earlier loss of bone tissue cannot be detected clinically or by routine radiology, but only by sophisticated bone density techniques.<sup>157-159</sup> Urist<sup>160</sup> and I<sup>161</sup> have independently derived the same diagnostic criteria based on radiological evidence of mobilization of trabeculae and vertebral deformity. Since the trabeculae or spongiosa are mobilized to a greater degree than the cortex, the vertebra in advanced cases gives the appearance of a hollow box. Earlier, the branching (secondary) trabeculae are lost. In an intermediate stage, the trabecular population is so reduced that one can actually count the primary trabeculae as he scans a lateral film of a vertebra. This appearance is in contrast to that of normal spongiosa which shows uncountable, intricately woven trabeculae. Because of the loss of spongiosa, the cortex, which is involved to a lesser degree, may actually give the false appearance of increased density. This leads to increased contrast between the cortex and spongiosa. In the post-menopausal variety of osteoporosis, the cortex is thin<sup>158,162</sup> but uninterrupted. Erosion of the cortex should make one think of malignant disease. In the osteoporosis of Cushing's disease, the superior and inferior plates are actually thickened or eburnated.<sup>35-37</sup> This appearance is pathognomonic of corticoid-induced osteoporosis. Various types of vertebral deformity may be seen. One is biconcavity due to bowing

of the superior and inferior vertebral plates by the pressure of the intervertebral discs. Localized invagination of a disc through the plate into the body of the vertebrae may occur; these are Schmorl's nodes. They are not restricted to osteoporosis, but occur in many vertebral diseases or developmental anomalies. Later wedge or compression fractures may occur. In osteoporosis the apex of the wedge fracture is anterior. Posterior wedging strongly suggests a different disease such as cancer, Paget's disease or trauma. Unlike fractures of other causes, vertebral fractures in osteoporosis generally do not cause neurologic complications. Naturally, immobilization should be minimized in any osteoporotic patient. In its earliest phase, only the weight-bearing vertebrae, from the eighth thoracic down, show involvement. A solitary fracture in a vertebra above this level strongly suggests a different cause, such as cancer, myeloma, epilepsy, electric shock therapy,<sup>163</sup> or trauma. Later, of course, when the entire spine is visibly involved, wedging may occur in the upper thoracic vertebrae as well. Fractures and kyphosis cause loss of stature, which is a useful index of new fractures.<sup>164</sup> Rather than obtain x-ray films of the entire spine at each examination, it is desirable to record exactly the patient's height and span. "If we measure from the sole of the foot to the top of the head, and apply the measure to the outstretched hands, the breadth will be found equal to the height" (M. Vitruvius Pollio, 27 B.C.).<sup>165</sup> In the absence of other conditions associated with decrease in height compared with span (arachnodactyly, hypogonadism or normal Negro proportions), vertebral fractures reduce height without affecting the span. Accurate measurement at each examination is a practical way of determining the presence of a new fracture.

*Other conditions.* With the diagnostic criteria listed here, one will not recognize early osteoporosis nor can it be recognized at present without sophisticated bone density techniques or bone biopsy. Onset of severe "osteoporosis" too soon after a normal menopause and involving too many vertebrae should make one think of neoplasm, osteogenesis imperfecta, or other disease. In the mild form of osteogenesis imperfecta, fractures stop at puberty and resume at the menopause. The presence of blue sclerae and spindly long bones may help in the diagnosis. Osteoporosis may co-exist with other causes of back pain, such as spondylolisthesis, vertebral osteophytosis, and acute back

sprains. The pain of these disorders should not be expected to respond to measures directed at controlling the osteoporosis.

*Treatment of the Osteoporoses.* In recent years multiple treatments have been suggested for osteoporosis. Bearing in mind that osteoporosis comprises a heterogeneous group of disorders, it is not surprising that no one treatment provides a panacea. For postmenopausal osteoporosis, estrogens and androgens have been advised (see below). Whether estrogens should be used prophylactically depends somewhat on the philosophy of the physician—whether he prefers to prevent or to treat disease. Davis et al.<sup>166</sup> and the Mcemas<sup>162</sup> have provided densitometric evidence that estrogen therapy significantly retards loss of bone substance in postmenopausal women. The use of estrogens and androgens in men, who far less commonly show osteoporosis by the criteria listed above, has been shown ineffective by the careful balance studies of Schwartz et al.<sup>167</sup> This group has shown that administration of large doses of calcium by mouth does indeed cause calcium retention, as previously reported by others.<sup>168,169</sup> Schwartz, however, pointed out that the calcium retention is not accompanied by phosphate retention, as it would be if bone mineral were being laid down.<sup>167</sup> Rose<sup>170</sup> denies that oral calcium produces positive calcium balance when carefully measured with chromium controls. He also notes that this treatment increases urinary calcium excretion and may precipitate renal calculi. Recently, Bartter and his co-workers<sup>171,172</sup> have studied the effects of intermittent calcium infusion to inhibit bone resorption in idiopathic osteoporosis. This investigation cannot be extrapolated to the therapy of either postmenopausal or corticoid-induced osteoporosis. Fluoride therapy has had a certain vogue based on the observation that inhabitants of areas with endemic fluorosis have dense bones.<sup>173</sup> The bone in fluorosis is not only dense, but brittle, and ectopic calcification—for example, painful peritendinitis calcarea—is common.<sup>174</sup> Since tea contains large amounts of fluoride, one might expect tea drinkers to be immune to osteoporosis, if this agent is really effective. Judging by the incidence of postmenopausal osteoporosis in the British Isles, I would guess that support for this thesis will probably not be forthcoming. Fluoride administration may produce slightly positive calcium balance<sup>175</sup> though this has been denied



by Rose.<sup>170</sup> Although fluorosis is characterized by increased bone density, it is not yet clear whether fluoride therapy benefits patients with the osteoporoses. It is also well established that fluorosis has toxic effects on bone<sup>176</sup> and elsewhere. At present, therefore, induction of fluorosis in patients with the osteoporoses can only be considered investigational.

With all these divergent treatments, it is evident that there is some dissatisfaction with present treatment of the various kinds of osteoporosis. Not surprisingly, the advent of calcitonin has raised therapeutic hopes. Experimental evidence is that calcitonin, like estrogens and androgens, inhibits bone resorption but does not stimulate bone accretion. Calcitonin has been tried in several forms of experimental osteoporosis in animals, without effect,<sup>177-179</sup> although it has been shown to retard osteolysis in intact rats.<sup>180</sup> In osteoporotic man, preliminary data suggest some calcium-retaining effect, unfortunately accompanied by evidence of parathyroid stimulation.<sup>181-183</sup> As pointed out above, calcitonin and sex hormones have the same action on bone, so that therapeutic effects can be expected to be similar.

*Estrogen Therapy of Postmenopausal Osteoporosis.* The use of estrogens for their ability to reduce bone breakdown in postmenopausal osteoporosis is now time-honored. Perhaps the reason their efficacy has been called into question is that too much was expected. They do not form new bone, increase bone density, relieve the mechanical sequelae of fractured vertebrae or correct preexisting deformities such as kyphosis. It is established only that they prevent progress of the disease. In 1947 Reifenstein and Albright reported a beneficial effect of estrogens and androgens on calcium balance in women with postmenopausal osteoporosis.<sup>10</sup> In a retrospective study of Albright's patients, Henneman and Wallach<sup>184</sup> showed that prolonged treatment with estrogens stops fractures and loss of height. Clinically, it is impressive that most osteoporotic women given estrogens note relief of pain, usually in the third week of treatment. This desirable subjective effect, however, cannot be taken as evidence of efficacy. In a carefully controlled study, using the double-blind Latin square technique, Solomon, Dickerson and Eisenberg found similar relief of pain and induction of wellbeing with an estrogen and a psychoactive placebo,

and even in half the patients treated with the inert placebo, lactose.<sup>185</sup> In this study it was shown that while the estrogen and androgen caused similar retention of calcium and of an exogenous strontium test load, the estrogen produced subjective wellbeing but the androgen did not. There was no connection between objective and subjective endpoints. In a twenty-year prospective study designed to compare the efficacy of estrogens with that of androgens and "anabolic" steroids (all weak androgens), various endpoints were sought.<sup>186</sup> It was found that relief of pain, reduction in urinary calcium or serum phosphate levels, induction of positive calcium balance and effects on skeletal kinetics, did not correlate with ability to prevent further fractures. The latter was therefore taken as the only conclusive evidence of objective efficacy. Obviously, such studies require long periods of observation, and the number of patients who can be studied is limited. The experimental design was that of the crossover, i.e. when a patient failed on one treatment or was unable to tolerate the agent, she was transferred to the other treatment group. In fact, however, the "crossover" ended in a one-way shift to estrogens, in large part because of the patients' intolerance of the androgenic effects of testosterone and its less androgenic "anabolic" derivatives. In twenty years of observation eight vertebral fractures occurred in 220 women receiving estrogens for 1,545 patient-years—a rate of five fractures per thousand patient-years. The vertebral fracture rate in 72 trials of androgenic-anabolic steroids for 202 patient-years was 40 per 1,000 patient-years, significantly worse than with estrogens ( $p < 0.01$ ). The minimal effective dose of estrogen was 1.25 mg of Premarin®, 50 µg of ethinyl estradiol, or 0.5 mg of stilbestrol daily for 25 days each month. Lower doses were ineffective in stopping vertebral fractures. Four of 220 women, who continued to have fractures on 1.25 mg of Premarin daily, required 2.5 mg of Premarin daily to prevent further fractures.

*Cyclic Estrogen Therapy does not cause Cancer.* In this study, too, the incidence of cancer was not increased by estrogen therapy. Because of the number of patients, their advanced age, and the number of years at risk, 18 cancers would normally have been expected. In fact, however, only six were seen and none of these was in the most common sites of female cancers, the cervix and breast. This study therefore

showed no evidence that cyclically administered estrogens in usual doses act as a potent carcinogenic stimulus. Thus, estrogen therapy of postmenopausal osteoporosis is effective in stopping the progress of the disease and does not increase the risk of cancer.

*Corticoid Induced Osteoporosis.* It is sad to think that 20 years after the introduction of corticoids for their anti-inflammatory effect, and despite 40 years of recognition of the osteoporosis of Cushing's disease, no treatment has been established for this condition. A single report of carefully controlled balance studies by Sprague et al in 1950<sup>187</sup> and an important abstract by Henneman et al in 1955<sup>188</sup> on the calcium-sparing effects of estrogen and androgen in 28 cortisone-treated asthmatics are the only studies known to this reviewer. These fragmentary data suggest that estrogens may reduce corticoid-induced bone breakdown in women, and androgens that of men. Calcium therapy was found ineffective in experimental osteoporosis produced by cortisone in rabbits.<sup>189</sup> Here clearly is an area where studies on pathophysiology and clinical pharmacology, and a rationale for good therapy, are needed. Meanwhile, clinicians can only keep the dose of corticoids as low as possible and avoid long-term, high-dose treatment for trivial indications.

### *Paget's Disease*

Paget's disease has recently come into the limelight because of rediscovery of the therapeutic benefit of antiosteolytic agents, in this case calcitonin, especially the very potent preparation from salmon ultimobranchial glands.<sup>70,190-193</sup> Paget's disease should probably not be called a disease in the majority of cases where it is found by accident, involves one or two bones and causes neither symptoms nor complications.

*Pathophysiology.* In its initial stages, best seen in the skull, it is characterized by a destructive process, misnamed osteoporosis circumscripta.<sup>194</sup> This destructive process spares the osteoblasts, causing a rise of alkaline phosphatase—unlike myeloma, which replaces osteoblasts and lowers the phosphatase level.<sup>195</sup> As a consequence, the resulting bony instability stimulates the osteoblasts to lay down more bone. Bony overgrowth in wild, unphysiologic patterns is seen on roentgenograms. Bowing and deformity occur in those

few patients who go on to a very far advanced stage of the disease. The nature of the underlying destructive processes is unknown. Because Paget's disease is rare before the age of 40 and is associated with increased vascularity, arteriovenous aneurysms and increased cardiac output, a vascular cause is suggested. Immobilization of patients with advanced Paget's disease causes the alkaline phosphatase level to fall, interpreted as a decrease in osteoblastic activity; urinary calcium excretion rises, indicating increased bone breakdown.<sup>196</sup> Since the rate of formation and destruction in widespread Paget's bone is astronomical, the adverse effect of immobilization on osteoblastic activity in the face of increased or exaggerated bone breakdown can lead to serious consequences, both local and remote. One of these is fracture of the immobilized bone. Another is the metabolic consequence of rapid bone breakdown: hyperealcemia and perhaps hypercalcemia. Immobilization is sometimes enjoined inappropriately in these patients because of painful, incomplete cortical fractures (infractures) that occur on the convex surface of bowed long bones.<sup>194</sup> These should not be immobilized since the pain disappears spontaneously and immobilization often leads to a true fracture. The danger of hypercalcemia in immobilization of even very widespread Paget's disease is probably exaggerated. My records show 64 immobilized patients with Paget's disease in the last 22 years. Naturally, they were closely observed for fear of hyperealcemia. In fact, however, the only patients in whom this was detected also harbored parathyroid adenomas! Both the local and metabolic dangers of immobilization, on the other hand, are real. Fractures and hyperealcemia are common<sup>197,198</sup> and renal calculi are frequent in such patients.

*Treatment.* When it comes to therapy, it has been reported that corticoids inhibit both the skeletal and cardiovascular processes.<sup>199</sup> The doses, however, are large and toxic. Twenty years ago, we reported that estrogens regularly reduce urinary calcium excretion and alkaline phosphatase levels in women with Paget's disease and androgens do the same in men.<sup>198,200,201</sup> These observations were soon confirmed by others.<sup>202,203</sup> The pain, which characterizes approximately a third of our cases of Paget's disease, disappeared during this treatment. We were reluctant to make much of the effect on pain since



it is well known that the pain of Paget's disease responds to almost any medical or surgical maneuver ever tried.<sup>204</sup> On the other hand the objective evidences of decreased alkaline phosphatase and urinary calcium excretion encouraged us to continue this treatment. While it is impossible to say that the course of the disease has been altered, pain has regularly been relieved and urinary calcium excretion has regularly declined. Similar results have been reported with aspirin,<sup>205</sup> fluoride,<sup>206</sup> calcitonin, and the toxic anti-tumor agent mithramycin.<sup>207</sup> The doses of estrogens used in women are the same as those used for postmenopausal osteoporosis—for example, Premarin® 1.25 mg, ethinyl estradiol 50 µg, or stilbestrol 0.5 mg daily for 25 days each month. In men testosterone cyclopentyl propionate (Depotestosterone®) or enanthate (Delatestryl®), 200 mg intramuscularly once a month reduce pain, calciuria and alkaline phosphatase levels. A similar antiosteolytic effect has been reported with porcine thyroid calcitonin<sup>70,192,193</sup> and with smaller doses of salmon ultimobranchial calcitonin.<sup>190</sup> Whether calcitonin injected frequently does anything that cannot be accomplished more easily by small doses of orally administered sex hormones remains to be seen.

*"Be not the first by whom the new are tried,  
Nor yet the last to lay the old aside."*

—Alexander Pope: Essay on Man.

#### TRADE AND GENERIC NAMES OF DRUGS

<i>Cortone® &amp; Cortef®</i> . . . . .	cortisone
<i>Diuril®</i> . . . . .	chlorothiazide
<i>Hydrodiuril® &amp; Esidrix®</i> . . . . .	hydrochlorothiazide
<i>Mithracin®</i> . . . . .	mithramycin
<i>Fluorouracil®</i> . . . . .	5-fluorouracil
<i>Dihydral®</i> . . . . .	dihydrotachysterol
<i>Amphojel®</i> . . . . .	aluminum hydroxide gel
<i>Premarin®</i> . . . . .	conjugated estrogens (equine)
<i>Estinyl®</i> . . . . .	ethinyl estradiol
<i>Adeflor®</i> . . . . .	fluoride
<i>Depo-Testosterone Cypionate</i> . . . . .	testosterone cypionate
<i>Delatestryl®</i> . . . . .	testosterone enanthate

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## TOLERABLE MILK INTOLERANCE

How do you treat milk or lactose intolerance?

"We limit the intake to the amount tolerated. Milk intolerance is not an allergy. Most of the people are able to drink milk in cereal or in coffee; they can drink it in small amounts. I have them limit the amount of ice cream and milk chocolate to the amount that would cause any symptoms. They also limit intake of powdered drinks, like Ovaltine® and Kool-Aid®, which are high sources of lactose. If patients want to drink milk, they can drink it in small amounts—a fruit juice glass three or four times a day. It seems to help if they take it with meals because gastric emptying seems to be delayed and the lactose gets a chance to be digested by whatever enzyme is present. It also helps if they don't take it iced, if they don't drink it right from the refrigerator. Icing a beverage will increase small intestinal speed of transit so that if the lactose is iced, it goes by so quickly that it doesn't get digested. Some of the fermented products, like yogurt and true cultured buttermilk, can be taken because the lactose has been split to lactic acid; some low-lactose-content milks are also on the market."

—THEODORE M. BAYLESS, M.D., Baltimore

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# Specialty Conference

## Research on the Diagnosis and Treatment of Myocardial Infarction

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THOMAS M. KAZAMIAS, M.D., JOHN ROSS, JR., M.D., PETER R. MAROKO, M.D.,  
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DR. E. BRAUNWALD:\* Arteriosclerotic coronary vascular disease is clearly the most important cause of death and disability in the modern Western world. It has been estimated that in the State of California alone during 1971 approximately 125,000 persons will have a myocardial infarction, that 60,000 will die as a consequence of this condition and that 17,000 of those who die will be under 65 years of age. An even larger number of patients will suffer from heart failure, angina pectoris and cardiac arrhythmias following recovery from a previous myocardial infarction.

Approximately five years ago, the late Dr. Robert P. Grant, then director of the National Heart Institute, recognizing the importance and enormity of the problem of acute myocardial infarction, initiated a series of actions designed to increase research to further our understanding of the acute infarction episode—its predisposing causes, recognition, estimation of severity, prognosis and therapy. I had the opportunity to discuss this program with Dr. Grant at its inception, and it is therefore particularly exciting for me to

observe the increasing interest among investigators throughout this country in this important condition, stemming in no small measure from Dr. Grant's vision.

It is the objective of this conference to discuss some of the efforts in the study and treatment of patients with arteriosclerotic coronary artery disease being carried out at the University of California, San Diego, School of Medicine. This conference serves as a follow-up to one held last year, at which we reviewed one aspect of these activities—the treatment of patients with intractable angina pectoris by means of electrical stimulation of the carotid sinus nerves.<sup>1</sup>

Despite important advances in the recognition of myocardial infarction by more careful physical examination, despite more refined electrocardiographic and vectorcardiographic criteria and the more ready availability of serum enzymes, such as the glutamic-oxalacetic transaminase (scot) and the creatine phosphokinase (CPK), it is still not uncommon to be faced with the clinical problem of whether or not a specific patient has suffered an acute myocardial infarction, and in patients who have chest pain during convalescence from an infarction whether or not an exten-

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sion has occurred. It is essential to sharpen our diagnostic criteria for a number of reasons, not the least of which is that the availability of acute coronary care facilities is limited, and their use is expensive. Drs. Karliner and Sobel have been interested in a recently recognized enzyme, glyceraldehyde phosphate dehydrogenase (GAPDH) and its use together with the isoenzymes of lactic dehydrogenase (LDH) in the solution of this important problem.

DR. J. S. KARLINER: \* Although the value of determinations of serum GOT, CPK and LDH in the diagnosis of acute myocardial infarction is well established, the sensitivity and specificity of these procedures have certain shortcomings, particularly with respect to prompt detection of extension of myocardial necrosis and early diagnosis of infarction. Accordingly, in conjunction with Drs. Sobel and Gander, assay of two alternative serum components, glyceraldehyde phosphate dehydrogenase (GAPDH) and LDH isoenzymes, was undertaken in patients with acute myocardial infarction. The results obtained were correlated with changes in conventionally determined serum enzymes in the same patient.<sup>2,3</sup> GAPDH is a glycolytic enzyme which catalyzes the phosphorylation of glyceraldehyde-3-phosphate. It occurs in the myocardium of several animal species, but assay of serum GAPDH activity has not previously been used as an index of myocardial necrosis in man.

Serum GAPDH activity was determined spectrophotometrically by a modification of Schmidt's procedure.<sup>4</sup> All hemolysed samples were discarded. The change in optical density of 340 millimicrons over three minutes, corrected for baseline activity, was used to calculate results, which we expressed as milli International Units per ml of serum. One milli International Unit is the amount of enzyme catalyzing the oxidation of one millimicromole of reduced nicotinamide adenine dinucleotide per minute. Lactic dehydrogenase isoenzymes were determined by disc gel electrophoresis.

In 54 fasting patients in hospital without clinical or laboratory evidence of recent myocardial infarction, the normal range for serum GAPDH activity was found to be  $16 \pm 13$  units (mean  $\pm$  S.D.). In 41 patients studied within 24 hours after the onset of acute myocardial infarction, serum GAPDH activity rose to an average 3.3 times control values. Although serum GAPDH activity

subsequently fell, values remained somewhat elevated for as long as 96 hours after the initial episode. From a practical standpoint, it is important that in 16 patients serum GAPDH activity was significantly increased 6 to 24 hours before serum CPK activity rose. Furthermore, in 18 patients serum GAPDH activity was increased before SGOT elevation began. On the other hand, serum GAPDH activity was within normal limits in only seven percent of samples obtained from patients studied within 24 hours of acute myocardial infarction.

The value of conventional serum enzyme determinations in detecting the extension of myocardial infarction in patients already convalescing from an acute episode has been limited, since persistent elevation of enzyme activity in serum may mask small rises reflecting further myocardial damage. The fact that serum GAPDH activity rises promptly following myocardial injury and the observation that elevated serum GAPDH activity persists for only a short time suggested that serum GAPDH determinations might be useful in the early detection of extension of acute infarction. Six patients demonstrated electrocardiographic and clinical evidence indicative of extension of myocardial infarction. In all of these, marked transient elevations of serum GAPDH activity occurred within hours in the face of unchanged or declining conventional serum enzyme values during the ensuing 24 hours.

Serum GAPDH activity was normal in 15 patients with angina pectoris admitted to the hospital because of chest pain who failed to exhibit diagnostic electrocardiographic or conventional serum enzyme changes indicative of myocardial infarction. However, in seven of thirteen patients with congestive heart failure manifested by pulmonary congestion, an abnormally elevated central venous pressure, and hepatomegaly, serum GAPDH activity was increased. Serum GAPDH activity was also elevated in 17 patients in hospital who were not initially selected for inclusion in the control group. The group included patients with hepatitis, alcoholism, metastatic malignant disease, pneumonia, pulmonary emboli and post-operative patients.

Isoenzymes, such as the well-known isoenzymes of LDH, are proteins existing as multiple molecular species, which are capable of catalyzing the same chemical reaction. LDH exists in five different such species which can be separated and quantified electrophoretically. Most organs

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have characteristic isoenzyme patterns. Heart, renal cortex, and red blood cells are rich in LDH isoenzymes one and two (LDH<sub>1</sub>, LDH<sub>2</sub>). Accordingly, it is not surprising that with myocardial or renal cortical injury, and with hemolysis, the levels of LDH<sub>1</sub> and LDH<sub>2</sub> rise in the serum, and in addition, the ratio of LDH<sub>1</sub> to LDH<sub>2</sub> increases. In our studies, this increase in the LDH<sub>1</sub> to LDH<sub>2</sub> ratio was used as an index of myocardial damage.

In 33 control subjects the normal range for LDH<sub>1</sub> to LDH<sub>2</sub> ratio was found to be  $0.70 \pm 0.18$  (mean  $\pm$  S.D.). In 54 patients with acute myocardial infarction, the average ratio was 1.07, ranging from 0.66 to 1.45. Only five patients in the entire group studied had an LDH<sub>1</sub> to LDH<sub>2</sub> ratio within two standard deviations of the normal mean. Two of these with a decidedly reduced cardiac index were in cardiogenic shock, a condition likely to lead to release of LDH isoenzyme components from skeletal muscle into the circulation. In 26 of 27 patients with acute myocardial infarction from whom sera were obtained within 24 hours after the onset of symptoms, the LDH<sub>1</sub> to LDH<sub>2</sub> ratio was abnormally elevated in the initial sample. This is of particular importance in view of the fact that in 18 of 54 patients total serum LDH activity in the initial sample was within the normal range.

The use of serum GAPDH activity as an index of extension of myocardial infarction in patients with definite initial damage may be of considerable practical importance. In this setting, the abnormal LDH isoenzyme pattern persists and hence is valueless in detecting extension of myocardial damage. However, because of the transient nature of serum GAPDH elevations, repetitive discrete increments in serum GAPDH activity in patients convalescing from myocardial infarction appear to provide a valuable objective index of extension of tissue damage.

Both indices considered together are valuable in establishing or excluding the diagnosis of acute myocardial infarction on the basis of the initially available blood sample. Thus, increased serum GAPDH without an elevated LDH<sub>1</sub> to LDH<sub>2</sub> ratio may be due to hepatic, musculo-skeletal, pulmonary, or neoplastic disease, as well as to congestive heart failure. On the other hand, although the LDH<sub>1</sub> to LDH<sub>2</sub> ratio once elevated may be persistently abnormal for a considerable period, the association of increased serum GAPDH

activity and an elevated LDH<sub>1</sub> to LDH<sub>2</sub> ratio strongly suggests acute myocardial infarction or extension of necrosis. Finally, the finding of normal serum GAPDH activity and a normal or decreased LDH<sub>1</sub> to LDH<sub>2</sub> ratio in the first blood sample available within 24 hours after onset of symptoms, offers strong evidence against the possibility that the patient has sustained an acute myocardial infarction.

DR. BRAUNWALD: Specifically, what are the potential clinical advantages of serial determinations of serum GAPDH compared with the more commonly used serum GOT and CPK?

DR. KARLINER: Elevations of serum GAPDH frequently appear earlier in patients with acute myocardial infarction than do those of serum GOT or CPK. Thus they may be used to confirm the diagnosis sooner than would be otherwise possible. Furthermore, since GAPDH elevations are both rapid and transient, assay of serum GAPDH activity is especially valuable in detecting myocardial damage in patients convalescing from the initial episode. Thus, serum GAPDH may rise, indicating extension, while serum GOT and CPK remain unchanged or continue to decline.

DR. BRAUNWALD: What about the method for serum GAPDH determinations—is it difficult to adapt for routine hospital laboratory use?

DR. KARLINER: The procedure is a simple spectrophotometric method, readily adaptable for routine use by either manual or automated techniques.

DR. BRAUNWALD: What about the routine measurement of the LDH isoenzymes?

DR. KARLINER: Conventional methods for LDH isoenzyme determinations are based on agar gel electrophoresis, disc gel electrophoresis (such as that used in our work), and differential DEAE absorption. The first two of these are readily adaptable for routine use at low cost. Automated procedures are only now becoming available.

DR. BRAUNWALD: We shall now turn to another important diagnostic problem in the patient with coronary artery disease; the differentiation between perfused and non-perfused areas of the myocardium. Selective coronary arteriography, of course, provides important information regarding the anatomy of the larger coronary arteries and outlines areas of obstruction in the coronary vascular bed. Coronary arteriography, however,

does not always provide information concerning the distribution of coronary blood flow to the small nutrient arterioles.

A number of years ago, in collaboration with Drs. William Ashburn, Dean Mason and others, we employed the Anger camera for radioisotope angiography<sup>5</sup> and became enormously impressed with the potential value of this approach in the characterization of cardiac structure and function. This experience, as well as the enormous clinical value of lung perfusion scanning following the injection of radioactive isotopes attached to macro aggregates of albumin, led to the application of similar techniques in the investigation of patients with coronary artery disease by means of myocardial perfusion scanning.

DR. W. L. ASHBURN: \* Myocardial perfusion scanning may be performed by injecting a known quantity of small radioactive particles into a coronary artery at the time of routine coronary artery catheterization and angiography. The distribution of the labeled macroaggregated albumin (MAA) particles throughout the myocardium is then determined by standard radionuclide imaging. The resulting myocardial images, obtained with a rectilinear scanner or scintillation camera, depict the relative distribution of myocardial blood flow at the precapillary level. This test, which is being employed both in this country<sup>6</sup> and in Japan,<sup>7</sup> is quite similar in concept to the familiar and widely used MAA lung perfusion scan. Both procedures are based on the observation that particles ranging in size from 10 to 60 micra in their greatest dimension will become lodged in precapillary vessels upon their introduction into the arterial supply to any organ. The distribution pattern of the particles is governed by the relative blood flow to each region of the organ which is perfused by way of the artery injected. A wide variety of radioactive particles can be used in organ perfusion scanning and, in each case, the resulting images reflect the overall perfusion pattern of the organ under study. Regional obstruction of blood flow is associated with a corresponding area of diminished concentration of radioactivity in the perfusion image. Since only a relatively small number of particles is injected as compared with the great abundance of precapillary vessels, no significant untoward physiologic effect from this degree of microembolization would be expected.

\* Associate Professor of Radiology; Head, Division of Nuclear Medicine.

Although the safety of lung perfusion scanning has been established by its widespread clinical use, we did not extend this technique to the evaluation of myocardial perfusion in humans until its safety was first determined in animals. The theoretical usefulness of the myocardial perfusion scan was originally suggested by the animal experiments of Quinn and his associates,<sup>8</sup> in which they showed regional reductions in radioactive particle distribution distal to experimentally occluded coronary vessels. Toxicity studies were carried out in our laboratory where it was determined that there was a wide margin of safety when the number and size of the particles injected were carefully controlled. In all dogs tested, 20 times the human equivalent dose of macroaggregated albumin particles failed to cause a significant alteration in recorded parameters of heart function. It was also shown that good quality images of regional myocardial perfusion could be obtained with as little as 0.05 mg of the denatured albumin particles labeled with technetium-99m (6 hour physical half-life; 140 kev gamma emission) or iodine-131 (8 day half life; 364 kev).

The ability to label these particles selectively with either radionuclide permitted separation of myocardial perfusion patterns via the right coronary artery circulation, following injection of <sup>131</sup>I MAA particles into the right coronary artery, from perfusion patterns associated with the injection of MAA labeled with <sup>99m</sup>Tc into the left coronary orifice by way of a selective percutaneous coronary artery catheter. Alternatively, the dual tracer technique was used to study separately the perfusion patterns before coronary artery branch occlusion in the dog using <sup>99m</sup>Tc MAA and following surgical occlusion using <sup>131</sup>I MAA, in which case a clear difference in regional perfusion could be seen.

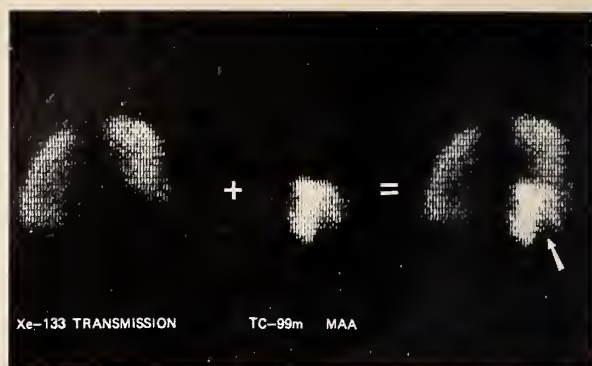
The myocardial perfusion scan was introduced as a clinical diagnostic method in the spring of 1970. Patients selected for the procedure usually presented with some form of suspected coronary artery disease for which coronary arteriography was indicated. Following the selective left coronary arteriogram, 0.02 mg of MAA labeled with <sup>99m</sup>Tc (approximately 300 microcuries) diluted with 5 ml of heparinized arterial blood was injected through the coronary catheter directly into the left coronary artery. This was followed by a



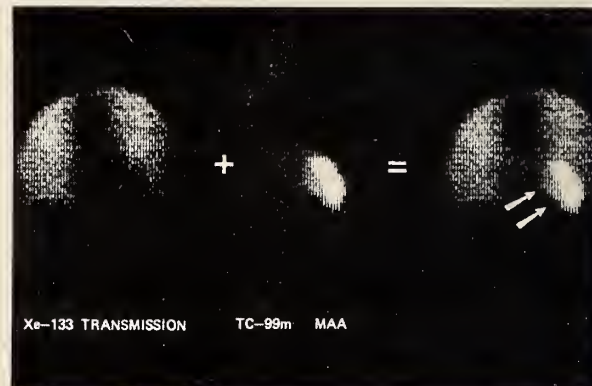
flush of saline and a small amount of contrast material to document the position of the catheter tip. Just before injection, a representative aliquot of particles was always examined under the microscope for proper size and consistency. During the time of the injection and for the next 10-30 minutes, the patient was monitored both by ECG and arterial pressure recordings. In no case have there been any detectable physiologic effects associated with the injection of the particles. Since these radioactive particles are cleared from the myocardium with a biologic half-time of approximately three to five hours, the myocardial perfusion images do not need to be obtained immediately. This permits continued observation of the patient while the catheters are removed and the arteriotomy is surgically repaired. While most patients are transferred from the catheterization laboratory to the nuclear medicine laboratory approximately 30 minutes following the selective injection of the particles, a period of up to several hours can elapse between injection and imaging.

Multiple views of the myocardium are obtained with the scintillation camera with the patient resting beneath the detector. Ordinarily, anterior, left lateral, left (LAO) and right (RAO) anterior oblique views are obtained. In some cases, a transmission image of the lungs is included by positioning the patient between a sealed sheet source of Xenon-133 gas and the detector of the scintillation camera to provide a reference image of the heart and mediastinal outline as contrasted with the extent of perfused myocardium viewed with the administered  $^{99m}\text{Tc}$  MAA. Each exposure of the scintillation camera is for that time necessary to collect approximately 50,000 to 100,000 counts (usually 2 to 3 minutes). Since there is no discomfort associated with the procedure, views can be repeated as often as necessary and other projections may be chosen. For convenience, but not a necessary part of the examination, the myocardial perfusion image data is also recorded in a digital computer format for subsequent detailed analysis.<sup>9</sup> This is in addition to the regular Polaroid images familiar to those used to viewing other organ scans—for example, lung perfusion scans.

A wide variation in myocardial perfusion patterns has been observed in the 22 patients studied so far. Perfusion abnormalities involving the circumflex coronary artery or one of its



**Figure 1.**—Abnormal  $^{99m}\text{Tc}$ -MAA myocardial perfusion scan in the anterior projection (center) in a patient having had three previous myocardial infarctions and electrocardiographic evidence of old anterolateral damage.  $^{133}\text{Xe}$  transmission scan (left) was obtained without moving the patient from beneath the detector. Computer addition of these previously recorded images produced a composite image (right) which allows better definition of the extent of hypoperfusion (arrow) involving the lateral wall of the heart. This area corresponded to a region of myocardial dyskinesis and was associated with complete obstruction of a marginal branch of the circumflex coronary artery. Injection of the particles was into the left coronary artery.



**Figure 2.**—Complete obstruction of the anterior descending branch of the left coronary artery (anterior projection). The distribution of the  $^{99m}\text{Tc}$ -MAA (center), injected into the left coronary artery, is seen in the lateral region of the heart where there is normal perfusion via the circumflex branch. Absence of radioactivity (arrows) along the anteromedial aspect of the composite image (right) indicates markedly reduced perfusion by way of the left coronary artery and resulted from obstruction of the anterior descending branch. The low left ventricle (D) pulsates paradoxically.

branches (Figure 1) are clearly distinct from diminished perfusion secondary to obstruction of the anterior descending branch (Figure 2). The correlation between the coronary arteriogram and the myocardial perfusion scan has been very good, with the former serving to demonstrate the gross anatomical features of the major arterial branches and the radioisotope study providing an overall image of relative regional myocardial

perfusion at the small vessel level. In addition, the myocardial perfusion scan has correlated well with other diagnostic methods such as left ventricular angiography and radarkymography, particularly in areas of myocardial dyskinesis where decidedly reduced perfusion has been demonstrated.

Although myocardial perfusion scanning is still in the clinical investigation stage, it appears promising as an additional tool for evaluating regional myocardial perfusion patterns in patients with coronary artery disease. It has been used in the preoperative evaluation of patients being considered for coronary artery bypass grafts and in the postoperative assessment of re-perfusion following surgical operation by selective injection of the particles into the graft. Using the same technique, but injecting a single coronary artery, this procedure may be used as an investigative tool in assessing the effects of non-surgical therapy on regional myocardial perfusion. Also, using the double radioisotope labeling technique, it may be possible to study the degree of collateral perfusion from either major coronary artery.

DR. BRAUNWALD: Aneurysm of the left ventricle is a well known complication of myocardial infarction, and has been recognized in about 35 percent of patients who have recovered from an acute attack. It has recently become clear from left ventricular angiocardiographic studies that wall-motion disorders occur in a much larger proportion of patients with chronic arteriosclerotic coronary vascular disease. Physical examination, fluoroscopy, roentgenkymography and indirect graphic techniques such as apex cardiography, electrokymography and kinetocardiography have suggested that wall-motion disorders may also occur in the presence of acute ischemia.<sup>10-13</sup> Does this also occur in patients with acute myocardial infarction, and if so are wall-motion disorders responsible for acute left ventricular failure and cardiogenic shock, the most dreaded complication of this disease?

In order to answer these questions one would like, obviously, to use non-invasive methods in the study of left ventricular wall motion in patients with acute myocardial infarction, since left ventricular angiocardiography might be too hazardous, and in any event cannot be repeated readily. Dr. Kazamias will now describe the application of a recently developed technique, radarkymography (which we originally employed

in the study of patients with valvular heart disease<sup>11</sup>) to the investigation of patients with acute myocardial infarction.

DR. T. M. KAZAMIAS: \* Left ventricular wall-motion abnormalities are known to exist in a variety of cardiac diseases. Most commonly they occur in patients who have had myocardial infarction and they appear during systole as localized "bulging" areas of the myocardial wall. Detecting and localizing them is of great importance since they interfere with the effectiveness of ventricular contraction and thus they may be a major cause of cardiac failure.<sup>15</sup>

With the development of radarkymography<sup>14</sup> a new, non-invasive technique has been available for recording cardiac wall-motion. It has advantages over the other techniques in that it is reproducible, it requires little radiation exposure, its response is linear and it does not rely on the subjective impressions of the observer. Furthermore, it is easily adaptable to acutely ill patients. Drs. Ross, Braunwald and I have found this technique to be of great clinical value in the study of wall-motion abnormalities in patients with acute myocardial infarction and various other forms of myocardial disease.

Radarkymography allows recording of wall-motion by tracking multiple areas of the heart border while the image of the heart recorded on videotape is scanned on a television monitor. The image of the heart on a television screen presents a change in density at the interface of the cardiac border and the lung. During ejection the heart border moves medially and during ventricular filling it moves laterally. Thus, it presents a constantly moving transition in density which creates a voltage peak onto which a tracker locks and follows the movements of the cardiac border. These movements in turn are translated into an analog signal, which can be displayed on an oscilloscope and the record has been termed the *radarkymogram*.

By manually positioning the tracker over various portions of the left ventricular silhouette, multiple areas can be tracked and their movements reproducibly recorded. The variations of the left ventricular and aortic radarkymograms of a 64-year-old man with an acute anterolateral wall myocardial infarction are shown in Chart 1. The electrocardiogram is shown above each radarkymogram. In panel A is shown the radarky-

\* Assistant Research Cardiologist.



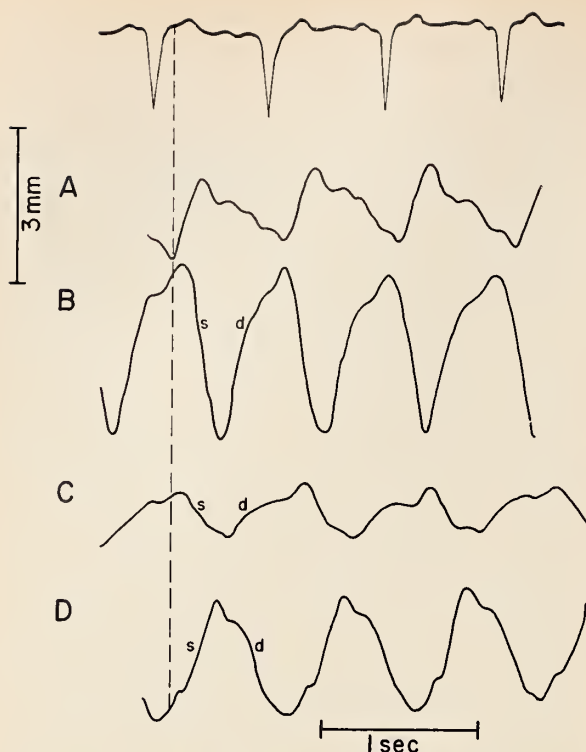


Chart 1.—Radarkymograms from a 64-year-old man with acute anterolateral wall myocardial infarction. The pulsations of the aorta (A) high (B) and mid (C) segments of the left ventricular (LV) wall are normal—that is, during systole in the ventricle there is a downward deflection and during diastole and upward deflection of the radarkymogram, while the aorta moves in the opposite direction. The mid-segment of the left ventricle (C) shows hypokinesis—that is, the movement of that segment does not exceed 1 mm.

mogram of the aorta. During ventricular systole the ejected blood distends the aorta, which moves laterally; this movement is recorded as an upward deflection on the radarkymogram. During diastole, when the aortic wall moves inward, the radarkymogram records a downward deflection. In panels B and C the radarkymograms of the high and mid-left ventricle are shown. During ventricular systole the heart moves medially and during diastole it moves laterally. The inward movement of the ventricular wall is recorded as a downward deflection on the radarkymogram and the outward movement as an upward deflection. The pulsations over the mid-left ventricle, however, (panel C) demonstrates hypokinesis, that is, the extent of the motion does not exceed 1 mm. Over the low left ventricle (panel D), the site of the acute myocardial injury, a paradoxical motion is recorded on the radarkymogram; that is, during systole, instead of

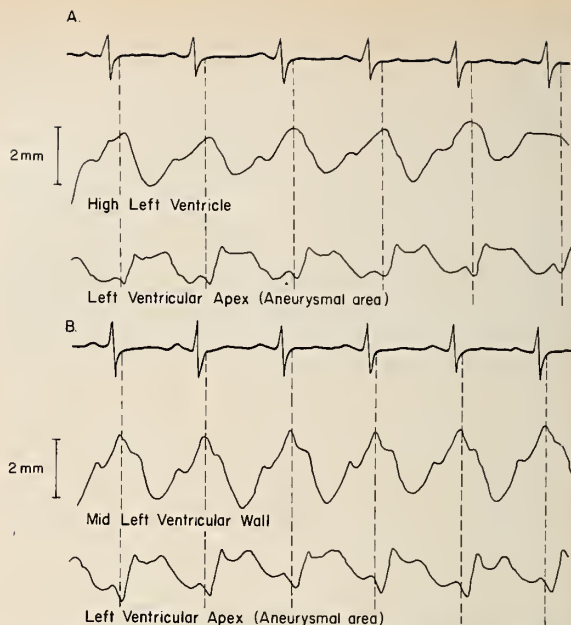


Chart 2.—Radarkymograms from a 73-year-old woman with an aneurysm involving the apical segment of the left ventricle. The high and mid left ventricle pulsate normally—a downward deflection on the radarkymograms represents inward movement of the left ventricle during systole and an upward deflection on the tracing represents outward movement of that segment during diastole. Tracings in the opposite direction are recorded over the aneurysmal area of the apex.

the normal downward deflection an upward deflection is recorded, and during diastole a downward instead of the normal upward deflection occurs. These abnormalities in the radarkymogram were followed semicontinuously for a follow-up period of up to six months.

Radarkymography has also been of great clinical value in assessing wall-motion abnormalities in patients who have recovered from a previous myocardial infarction. Chart 2 shows the radarkymograms obtained in a patient who had an acute inferolateral wall myocardial infarction two years before study. In panel A the radarkymogram from the high left ventricle is compared with that obtained simultaneously from the left ventricular apex, where an aneurysm was present. In panel B the tracings from the mid-ventricular wall are again compared with those of the ventricular apex. Both the high and the mid portions of the left ventricle pulsate normally; that is, during systole when the heart moves medially, a downward wave is recorded on the radarkymogram and in diastole, when the heart moves laterally, an upward deflection is recorded. A complete reversal in pulsation is re-

corded over the aneurysmal area of the apical segment of the left ventricle. The presence of a large apical aneurysm in this patient was subsequently confirmed by left ventriculography.

In three-fourths of patients with acute myocardial infarction paradoxical pulsations of the left ventricular wall were recorded by means of radarkymography. In seven-eighths of patients with chronic coronary artery disease, with or without old myocardial infarctions, paradoxical pulsations were demonstrated.

Abnormal wall-motion also was demonstrated in all three patients with various forms of primary myocardial disease whom we have studied to date.

These studies show that radarkymography is an effective and reliable non-invasive technique with which wall-motion abnormalities can be detected accurately in ambulatory subjects, as well as in acutely ill patients. Its clinical value is enhanced by the fact that it can be used in a coronary care setting in which wall motion abnormalities can be identified early in acute myocardial infarction, and their progression or regression then can be followed over a prolonged period of time.

DR. BRAUNWALD: When we contemplate the possibility of surgical and other newer forms of treatment of acute myocardial infarction, we are most anxious to establish an accurate prognosis. A number of factors are of importance—the patient's age, the number of previous infarcts, his functional state, the presence of diabetes mellitus, hypertension and the like. All of these are helpful when one attempts to predict the outcome in a large population of patients, but none have great predictive value in an individual patient. Drs. Ross, Gander and Kazamias have developed a relatively simple, but intriguing approach to this problem.

DR. J. ROSS, JR.:\* The determination of overall cardiac size is important in the assessment of patients with heart disease and may be of considerable value in evaluating patients with acute myocardial infarction. It seemed likely that estimation of the size of the left heart could prove even more useful, and we therefore sought to develop a non-invasive, yet reliable method for the serial assessment of left ventricular size in acutely ill patients.

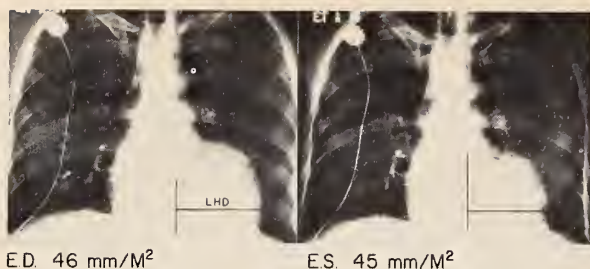
\*Professor of Medicine; Director, Myocardial Infarction Research Unit.

We postulated that the distance between the left border of the spine and the left heart border (termed the left heart dimension, LHD) should be relatively free from the influence of right heart filling and therefore should reflect alterations in the size of the left ventricle. Subsequently, we measured the LHD at end diastole using an ECG-synchronized x-ray system, and compared it with the left ventricular cavity size determined by left ventricular angiocardiography. The latter was measured as the perpendicular to the mid-point of the long axis of the left ventricle which was drawn from the mid-plane of the mitral valve to the apex of the left ventricle. Changes in left ventricular size were induced acutely in patients undergoing cardiac catheterization by changing the resistance to left ventricular ejection with agents such as methoxamine or arfonad, and alterations in LHD and the angiocardiographically determined left ventricular cavity size were compared; the correlation coefficient relating these two variables was 0.922.<sup>16</sup>

We then applied this simple radiographic technique to determine the normal LHD in 50 subjects with no known cardiovascular disease. The ECG-synchronized roentgenograms were exposed at end diastole in the respiratory mid-position, with the subject positioned in bed and the upper half of the torso at 45° from the horizontal. The range of normal values (corrected for x-ray magnification) for LHD per square meter ( $M^2$ ) of body surface area ranged from 26.2 to 40.5 mm (mean =  $32.8 \pm 8.2$  mm/ $M^2$ ,  $\pm 2$  S.D.).<sup>16</sup> Variations in heart rate between 55 and 100 per min did not have a significant effect on this measurement; the reproducibility of the method was tested in 25 patients on different days and the average variation was 1.1 mm/ $M^2$ .

This approach was then applied to assess serial changes in left heart size in patients admitted to the hospital with unequivocal evidence of acute myocardial infarction.<sup>17</sup> When initially studied within 24 hours after myocardial infarction some patients had normal values for LHD, which either remained normal during the follow-up period of up to 16 months or became abnormal. For example, Figure 3 shows the roentgenograms in a 52-year-old man obtained following acute myocardial infarction. When first studied six hours after the onset of symptoms, the LHD in this patient was 36.2 mm/ $M^2$ , well within normal limits; six weeks later, however, the LHD was grossly in-





**Figure 3.**—Roentgenograms obtained in a man who had an acute myocardial infarction six weeks earlier. Six hours after the onset of symptoms his left heart dimension (LHD) was 36.2 mm per square meter. In six weeks it became grossly abnormal, measuring 46 mm/M<sup>2</sup> at end diastole (ED), *left*, and 45 mm/M<sup>2</sup> at end systole (ES), *right*.

creased. In other patients, the initial values of LHD were abnormal and either remained so for a period of up to six months or became normal.

Forty patients have now been followed for six weeks to 16 months following acute myocardial infarction. All 25 patients in whom the left heart size was normal at the end of the follow-up period, regardless of whether or not it was enlarged during the acute episode, have survived. Of the 15 patients whose left heart size was initially enlarged or became abnormal 11 (73 percent) have died, and only 4 (27 percent) are survivors. Whether or not this trend will continue as a larger and more diverse group of patients is studied over a longer time period remains uncertain.

Our findings indicate that this approach provides a practical, accurate, and non-invasive method for obtaining serial estimates of left ventricular size. Although the mechanism of late death in patients with cardiac enlargement remains unclear, a persistently abnormal left heart dimension following acute myocardial infarction appears to have highly important prognostic implications.

**DR. BRAUNWALD:** The mortality from acute myocardial infarction results from two major factors: disturbances in rhythm and power failure. Although in-hospital deaths from cardiac arrhythmias have decreased substantially as a consequence of improved monitoring and prompt treatment, the mortality due to power failure, particularly associated with cardiogenic shock, is still high and is now responsible for the majority of in-hospital deaths from acute myocardial infarction. Moreover, chronic heart failure is a major complication in patients who survive the acute episode. Therefore considerable investiga-

tive efforts have been devoted to the study of the effects of power failure on the peripheral circulation, and therapy has been aimed primarily toward improving peripheral pressure or blood flow or both. A different approach to the treatment of acute power failure is the reduction of the impairment of cardiac contractility. One such proposal, for instance, involves resection of the dyskinetic area of myocardium resulting from an infarct which impairs left ventricular function. Another possible therapeutic approach is to limit the size of the infarct which develops following coronary occlusion and to maintain the maximal quantity of viable myocardium.

Some clinical observations suggest that factors which influence the balance between myocardial oxygen supply and demand may aggravate or alleviate the symptoms of myocardial ischemia. Thus, beta adrenergic blockade, carotid sinus nerve stimulation, treatment of hyperthyroidism and reduction in the size of a dilated heart, interventions which tend to reduce myocardial oxygen demands, frequently improve symptoms of myocardial ischemia.<sup>1</sup> Conversely, fever, hypertension, tachycardia, acute anemia and the treatment of hypothyroidism—that is, interventions which augment myocardial oxygen demands—aggravate these symptoms in patients with coronary artery disease. A major effort in our laboratories during the past two years has been to examine the hemodynamic conditions and pharmacologic interventions which might alter the size of an infarct by changing the balance between oxygen supply and demand in and around the area of myocardium supplied by the occluded vessel.<sup>18</sup> The goal of these studies has been to determine the influence of various commonly used drugs and interventions on the size of the infarct. Special emphasis was placed on finding interventions which would be beneficial by reducing the quantity of infarcted myocardium and maintaining the viability of cardiac tissue following coronary occlusion.

**DR. P. R. MAROKO:**\* At the commencement of these studies we required a precise and reproducible measure of the quantity of damaged tissue. We noted in preliminary experiments that standard pathologic techniques are not suited for elucidating the effects of hemodynamic and pharmacologic interventions on the extent of myocardial infarction. Pathologic and biochemical

\* Assistant Clinical Professor of Medicine.

determination of the size of an infarct provide little information for at least six hours following coronary occlusion<sup>19</sup> and serious arrhythmias and pronounced hemodynamic changes, which might by themselves alter the size of the infarct, often occur during this period. Moreover, there is considerable variability in the coronary arterial distribution in different dogs, making it difficult to compare the effects of ligating the same vessel in different animals.<sup>19</sup> We circumvented these difficulties inherent in evaluating the size of the injured zone of myocardium immediately following coronary ligation by examining the extent and magnitude of epicardial ST segment elevation in areas surrounding the coronary occlusion.<sup>18</sup>

This technique allows rapid and reproducible determination of ischemic cellular injury in the same animal, permitting the use of each dog as its own control. Essentially, it consists of recording epicardial electrocardiograms in ten to fourteen anatomically recognizable sites in open-chest anesthetized dogs. These sites are selected so that some are clearly in the region in which perfusion is dependent on the vessel to be occluded, and others are completely outside this area. The left anterior descending coronary artery or one of its branches was occluded for 20 minutes, always allowing at least an hour for recovery between separate occlusions. ST segment elevation in all sites was measured before and 5, 10, 15 and 20 minutes after occlusion. This ST segment elevation was used to quantify myocardial ischemic injury. Two indexes were used: (1) Average ST segment elevation in millivolts ( $\overline{ST}$ ) which indicates the magnitude of the injury; and (2) the number of sites at which ST segment elevation exceeded 2 mv (NST), representing the extent of injury. The first occlusion was always done without any other intervention (simple occlusion) while subsequent occlusions were performed while administering drugs or altering hemodynamic conditions. The values of  $\overline{ST}$  and NST were compared in order to assess the changes in the extent and magnitude of myocardial ischemic injury due to the pharmacologic or hemodynamic intervention.

This experimental protocol offers many advantages: The time that elapses between the occlusion and the study of the results is short, which eliminates the influence of complicating factors such as arrhythmias. The ischemic injury produced is completely reversible as judged by elec-

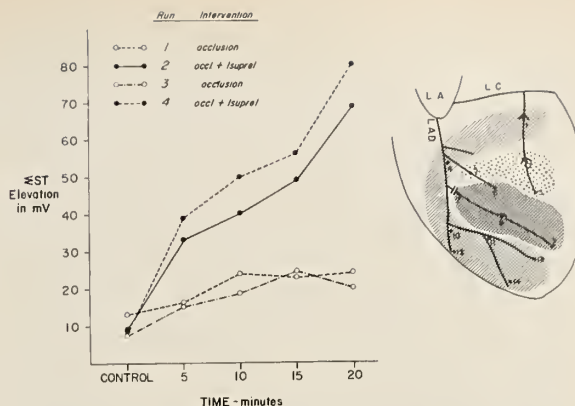


Chart 3.—Effects of occlusion alone and occlusion following the infusion of isoproterenol (0.25 ug/kg/min). L.A.D. = left anterior descending coronary artery. L.C. = left circumflex coronary artery. LA = left atrium. Cross hatched area: Area of injury after 15 minutes of occlusion. Stippled area: The increase of area of injury when the occlusion was performed under the influence of isoproterenol. Lined area: Area that showed no ST segment elevation under any conditions. Reproduced by permission from *Circulation* 43:67, 1971.

trocardiography as well as by biochemical and histological studies.<sup>20</sup> Consequently, as seen in Chart 3, ST segment elevation is reproducible when several repetitive occlusions are carried out in the same animal. This reproducibility is observed in simple occlusions (Chart 6, runs 1 and 3) as well as in occlusions with an intervention (for example, isoproterenol, runs 2 and 4 in Chart 3). Consequently, this method offers the unique advantage of using each animal as its own control, thus eliminating the problem of comparing dogs with different coronary arterial distributions.

Several lines of evidence support the validity of using the epicardial ST segment as a measurement of myocardial injury. Good correlation has been reported between the height of epicardial ST segment elevation and the magnitude of ischemic alterations of myocardial cellular membrane potential<sup>21</sup> as well as the reduction of intramyocardial  $pO_2$  several minutes following coronary occlusion.<sup>22</sup> Moreover, the area of ST segment elevation always coincides with the region of the heart which becomes visibly cyanotic after occlusion. A close correlation between ST segment elevation and the prevalence of anaerobic metabolism has been demonstrated<sup>23</sup> and as will be discussed by Dr. Sobel below, there is an excellent correlation between ST segment elevation and myocardial CPK depletion.



The results of experiments conducted in 118 dogs<sup>18,24-26</sup> show that in the nonfailing heart interventions that increase myocardial oxygen consumption, such as tachycardia and a variety of positive inotropic drugs, increase the size of the zone of ischemic injury, whereas interventions which lower myocardial oxygen consumption decrease it. Thus, administration of isoproterenol (0.25-0.50 mg per kg per min) in nine dogs increased the extent and magnitude of myocardial injury.  $\overline{ST}$  rose from an average of 1.6 to 6.0 mv and NST from an average of 2.2 to 7.0 when the simple occlusion was compared to occlusion carried out during the administration of isoproterenol. It is felt that the observed changes were due to an intensification of ischemic injury, since sites remote from the occluded vessel never showed ST segment elevation, even following isoproterenol, and the infusion of these quantities of the drug into dogs without coronary occlusion also failed to produce ST segment elevation.

Tachycardia, produced by electrical stimulation in three experiments, also increased myocardial injury. However, this increase was less than that produced when comparable heart rates were produced by isoproterenol, indicating that the increase in myocardial ischemic injury produced by isoproterenol is only partially due to the increase in heart rate, its positive inotropic effect probably accounting for the additional increase.

Ouabain (0.03 mg per kg) was given to six animals with a nonfailing heart and increased ST from 2.2 to 4.1 mv, while NST increased from 5.0 to 7.2. Thus this digitalis glycoside, which augments the oxygen requirements of the nonfailing heart, clearly increases the severity and extent of myocardial injury following coronary occlusion. In six other experiments, the same dose of ouabain was administered to dogs with pharmacologically produced acute depression of left ventricular function, in which a coronary artery occlusion was also carried out. In these circumstances digitalis is known to reduce myocardial oxygen consumption<sup>27</sup> and myocardial ischemic injury decreased ( $\overline{ST}$  decreased from 4.2 to 1.5 mv). These observations emphasize that any particular intervention may have different and even opposite effects on the severity and extent of myocardial damage after coronary occlusion, depending on left ventricular function. This can be understood by considering the determinants of oxygen consumption.<sup>27</sup>

Glucagon (5-20 ug per kg) increased the myocardial ischemia in 4 dogs.  $\overline{ST}$  rose from 3.4 to 8.0 mv and NST from 3.5 to 6.0. As in the case of isoproterenol, this increase was, in part, due to tachycardia. Bretylium tosylate has been recommended for use in acute myocardial infarction because of its combination of antiarrhythmic and positive inotropic properties. However, in two experiments (5 mg per kg) this agent also increased myocardial injury. Thus, bretylium, like the other positive inotropic drugs, independent of the mechanism of this effect, causes an augmentation of tissue injury in the nonfailing heart.

On the other hand, interventions which reduce myocardial oxygen consumption have been observed to reduce the magnitude and extent of myocardial ischemic injury. Thus, propranolol (0.5-2.0 mg per kg) decreased the injury. In eight dogs so studied,  $\overline{ST}$  decreased from 3.9 to 1.6 mv and NST from 5.4 to 1.1. Similar results were obtained in six dogs with practolol (2.5 mg per kg), a cardio-specific beta-adrenergic blocker which does not possess the nonspecific negative inotropic effect of propranolol.  $\overline{ST}$  decreased from 4.5 to 2.4 mv and NST from 8.3 to 4.5. Thus, both beta blocking agents appeared to protect the myocardium from ischemic injury after coronary occlusion.

Counterpulsation with an intra-aortic balloon in nine dogs showed that this procedure, which decreases left ventricular afterload and increases coronary flow, produced a substantial decrease in myocardial injury.  $\overline{ST}$  decreased from 3.3 to 1.4 while NST decreased from 7.8 to 4.0.

Another series of studies examined the influence of arterial pressure on myocardial injury. Arterial hypotension (six animals) caused an increase in myocardial injury;  $\overline{ST}$  increased from an average of 2.8 to 9.0 mv and NST from 1.8 to 6.3. Conversely, elevating arterial pressure by the administration of methoxamine reduced myocardial injury,  $\overline{ST}$  decreasing from 4.9 to 1.6 mv and NST from 4.4 to 2.1. The inverse relationship between arterial pressure and the magnitude of myocardial injury is illustrated in Chart 4; repetitive occlusion were performed in 4 dogs at various levels of arterial pressure. When arterial pressure was elevated, the increase in the supply of oxygen to the myocardium due to the augmentation of coronary perfusion pressure exceeded the increase in oxygen demands which result from raising the wall tension.<sup>28</sup> In the case

## EFFECT OF ARTERIAL BLOOD PRESSURE

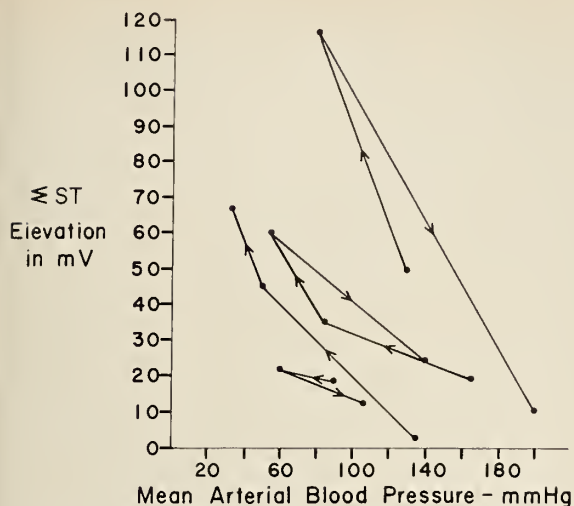


Chart 4.—Relationship between arterial pressure and myocardial injury.  $\Sigma$ ST 15 minutes following an occlusion at three to four different levels of mean arterial pressure. Each group of connected points represents one animal.  $\Sigma$ ST is the sum of ST segment elevations at all epicardial sites.

of arterial hypotension the reverse situation was obtained.

In another series of experiments it was shown in closed-chest dogs with sustained coronary occlusions that myocardial ischemic injury can be altered by interventions such as isoproterenol, propranolol and methoxamine up to six hours following occlusion. In these dogs alterations in the extent and severity of myocardial injury similar to those described above for acute occlusions were observed.

An intervention which acts through a different though not yet completely understood mechanism to limit the extent of myocardial necrosis following coronary occlusion is the infusion of glucose-insulin-potassium solution. Presumably by increasing the energy available to the myocardium through anaerobic glycolysis, myocardial tissue survives even though rendered ischemic.<sup>25</sup> In control (non-treated) dogs all sites with significant ST segment elevation 15 minutes following coronary occlusion showed morphologic signs of myocardial necrosis 24 hours later. In contrast, almost half the sites with similar ST segment elevations obtained from dogs with coronary occlusion and treated with glucose-insulin-potassium were normal. Also, the extent of myocardial CPK depression, to be discussed by Dr. Sobel, was

smaller than that expected from the epicardial ST segment elevation.

DR. BRAUNWALD: The studies by Drs. Maroko, Sobel and colleagues indicate that the amount of tissue damage as a consequent of acute coronary occlusion may be altered by changes in the balance between myocardial energy supply and demand. Thus in the presence of an occlusion the myocardium can be protected from injury by an increase in oxygen supply (arterial hypertension) or by a reduction in oxygen demands (propranolol, practolol) or both of these influences acting simultaneously (arterial counterpulsation). Energy supplies may also be augmented by glucose-insulin-potassium infusion. Despite the obvious differences between these experiments and the clinical situation, the results of these investigations suggest that for several hours following a coronary occlusion the potential size of an infarct can be reduced. On the other hand, the use of positive inotropic drugs, especially in patients without cardiac enlargement and failure, may be deleterious to the survival of myocardial cells in the areas immediately surrounding the zone supplied by the occluded vessel. The importance of controlling heart rate, and of maintaining arterial pressure, in preventing extension of necrosis in patients with coronary occlusion is evident. These observations also serve to explain the vicious cycle set up in patients with acute myocardial infarction by a reduction of arterial pressure: By decreasing coronary perfusion pressure, hypotension increases myocardial damage, resulting in further reductions in cardiac output and systemic arterial pressure.

One of our major research goals has been to develop methods of measurement of the extent of tissue damage following myocardial infarction and to examine the effects of pharmacologic and physiologic interventions on tissue necrosis. Despite the efforts of many investigators using a variety of experimental animal preparations, a convenient, accurate biochemical index of the extent of cardiac necrosis following experimental myocardial infarction is not yet available.<sup>29</sup> During the past two years Dr. Sobel has examined changes in activity of several myocardial enzymes following coronary artery occlusion in order to develop such an index and he will now summarize his findings.

DR. B. SOBEL: \* Initial studies in rabbits revealed

\* Assistant Professor of Medicine; Director Coronary Care Unit.



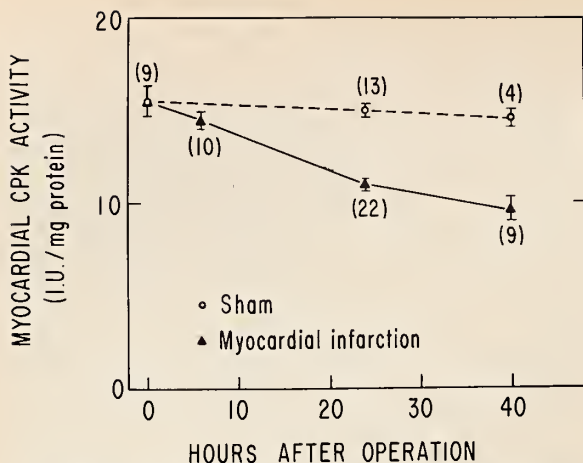


Chart 5.—CPK activity in whole left ventricular homogenate. Myocardial CPK activity (mean  $\pm$  S.E.) in homogenates prepared from the whole left ventricles of sham-operated rabbits (o) and those with coronary occlusion ( $\Delta$ ) six, twenty-four and forty hours following operation. The number of experiments is indicated in parentheses. Reproduced by permission from *Circulation Res* 27:403, 1970.

that the changes in activity of most myocardial enzymes in infarcted or ischemic tissue are variable 24 hours after coronary artery occlusion. This probably reflects contributions to total measured enzyme activity of inflammatory infiltrate, and of endothelial and fibroblastic elements in the heart as well as of the myocardium itself. Since creatine phosphokinase (CPK) is found predominantly in skeletal muscle and myocardial cells,<sup>30</sup> it was considered likely that depressed myocardial CPK activity would be useful as a relatively specific index of the extent of ischemic injury.

Results obtained in experiments designed to explore this hypothesis demonstrated that: (1) myocardial CPK activity is consistently and characteristically reduced in homogenates from the whole left ventricle 24 hours following coronary artery occlusion; (2) the extent of reduction of myocardial CPK activity in a specific sample of myocardium is directly related to the extent of reduction of blood flow measured with the use of radioactive microspheres; (3) the time course of reduction in myocardial CPK activity corresponds well with typical changes of CPK activity in human serum following myocardial injury; and (4) similar results are obtained whether myocardial CPK activity is measured with a conventional assay utilizing coupling enzymes or is measured by assay of phosphate released from creatine phosphate in an assay system independent of coupling

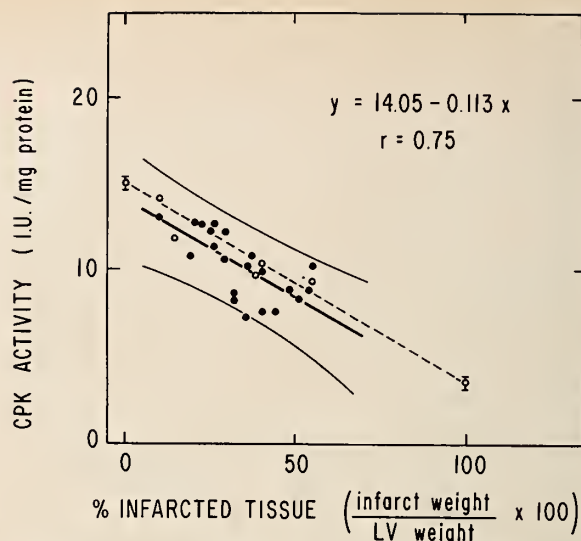


Chart 6.—The correlation between myocardial CPK depression and infarct size. CPK activity was measured in whole left ventricular homogenates and infarct size was determined by weight. Solid circles represent infarct cut out on the basis of the endocardial hemorrhagic border. Open circles indicate those excised on the basis of multiple sections through the myocardium. The regression line (least squares method) is represented as a solid line; 95 percent confidence limits are shown. The means  $\pm$  standard error of CPK activity in homogenates from normal tissue and from the center of infarcts are indicated by open circles and vertical lines. The broken line connecting these represents the hypothetical relationship between CPK activity and infarct size, assuming that this relationship is linear. As can be seen, the regression line derived from experimental data conforms quite closely to this hypothetical linear relationship. Reproduced by permission from *Circulation Res* 27:403, 1970.

enzymes. Results from some of these experiments are shown in Charts 5 and 6 and indicate the depression of myocardial CPK activity is an accurate, sensitive, and convenient index of the extent of tissue necrosis following coronary artery occlusion.<sup>31</sup>

Encouraged by these findings, and in collaboration with Doctors Maroko, Watanabe, Covell, Ross and Braunwald, we subsequently utilized myocardial CPK activity as an index of tissue necrosis in a study exploring the effect of hemodynamic and pharmacologic factors on the extent and severity of tissue damage following coronary artery occlusion in dogs.<sup>18</sup> By combining the epicardial mapping technique, previously described by Dr. Maroko, with analysis of myocardial CPK activity 24 hours later, it was possible to use each dog as its own control. Thus, epicardial ST segment maps were obtained immediately following coronary artery occlusion and used as an index

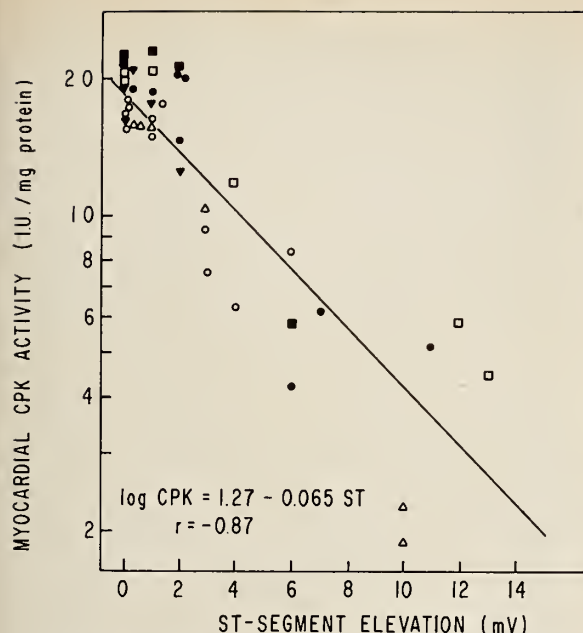


Chart 7.—Myocardial CPK depression and epicardial s-T segment elevation in the dog. Epicardial recordings were obtained 15 minutes after coronary artery occlusion from readily identifiable sites. CPK activity was measured in homogenates from full wall biopsies obtained from the same sites 24 hours later and is expressed on a logarithmic scale. Multiple samples were obtained from six dogs. Corresponding symbols represent samples from the same dog. Reproduced by permission from *Circulation* 43:67, 1971.

of anticipated myocardial necrosis. The intervention under study was then applied, and 24 hours later myocardial CPK activity was determined in samples corresponding to points previously mapped. As shown in Chart 7, ST segment elevation accurately predicts the subsequent CPK depression expected 24 hours following coronary artery occlusion in the absence of a pharmacologic or physiologic intervention.<sup>18</sup> Thus, CPK depression in excess of that anticipated from the epicardial electrocardiogram in a given sample provides an index of the extent to which an intervention increases tissue necrosis following coronary artery occlusion. Conversely, less CPK depression than that expected from the ST segment map indicates that an intervention exerts a protective effect. Dr. Maroko has previously summarized the effects of several interventions on epicardial ST segment maps. Myocardial CPK depression correlated with these findings consistently. Thus, infusion of isoproterenol increased the extent of myocardial CPK depression anticipated on the basis of epicardial ST segment measurements (Chart 8) while propranolol de-

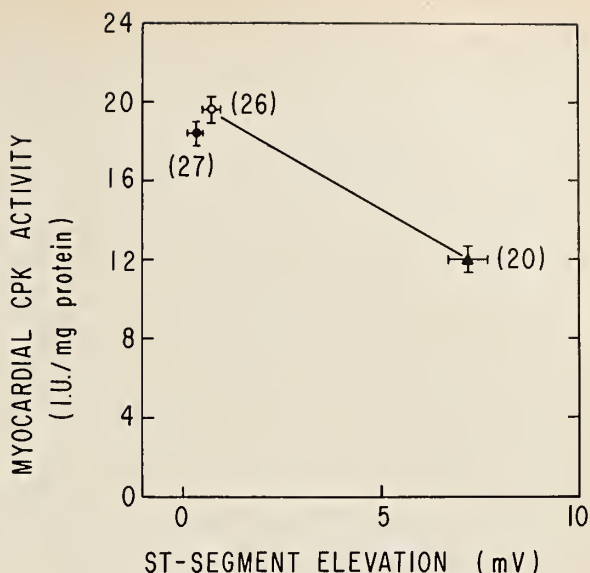


Chart 8.—Augmentation of the area of epicardial s-T segment elevation and myocardial CPK depression after coronary artery occlusion accompanied by isoproterenol in the dog. Values represented are means  $\pm$  S.E.M. (0) = values in nonischemic tissue from six dogs receiving no isoproterenol. (0) = values from sites without s-T segment elevation in animals subjected to coronary artery occlusion and given isoproterenol. ( $\Delta$ ) = values in the same animals from sites with no s-T segment elevation after coronary artery occlusion but with s-T segment elevation after occlusion plus isoproterenol administration. The results demonstrate that myocardial CPK depression occurred in these sites within 24 hours.

creased myocardial CPK depression (Chart 9). Thus, the evidence suggests that isoproterenol increased the severity and extent of ischemic injury while propranolol exerted a protective effect.

Since myocardial CPK activity is a valid index of the extent of necrosis following coronary artery occlusion, studies have been undertaken to apply this information to patients. In order to accomplish this aim, it is first necessary to define the relationship between changes in serum CPK activity and myocardial CPK activity following coronary artery occlusion under controlled conditions. Accordingly, with Drs. Kjekshus and Shell, the kinetics of dog heart CPK have been measured in serial serum samples. Changes in serum CPK following coronary artery occlusion have been compared with myocardial CPK depression in the same dog 24 hours later and the relationship between changes in serum CPK and in myocardial CPK following the imposition of physiologic and pharmacologic interventions has been examined.<sup>32</sup> On the basis of studies with dog heart CPK, purified according to Noda et al,<sup>33</sup>



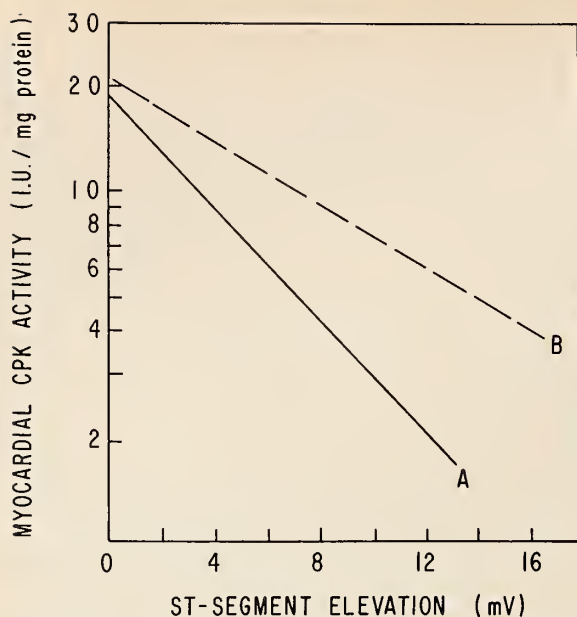


Chart 9.—*Diminished myocardial CPK depression following administration of propranolol in dogs with coronary artery occlusion.* Data from multiple samples from six animals given propranolol (0.5 to 2.0 mg/kg) were pooled.

A. Regression line for control study (see Chart 7) (Log CPK =  $1.269 - .065 \text{ ST}$ ,  $r = -.87$ .)

B. Regression line for S-T segment elevation following coronary artery occlusion before the drug was given and log CPK from corresponding sites 24 hours later. (Log CPK =  $1.302 - .035 \text{ ST}$ ,  $r = -.53$ .)

Thus, in animals that had received propranolol, depression of myocardial CPK activity was less than that which would be expected from S-T segment elevation occurring before drug administration.

and injected into normal animals, a characteristic monoexponential serum CPK disappearance curve was defined. The fractional disappearance rate (kd) averaged .005 per minute (normal = .010). This value was virtually identical to that observed when animals were subjected to coronary artery occlusion and serial serum CPK determinations were performed. After an initial lag period and the subsequent appearance phase, the endogenous CPK disappearance curve approached a monoexponential pattern with kd averaging .004 per minute ( $n=7$ ). On the basis of mathematical analysis of data obtained during appearance phase and interpreted in the light of the known kd, accurate estimates for total CPK released from the myocardium following coronary artery occlusion could be obtained by means of serial serum CPK determinations.

In nine experiments in which myocardial CPK depression was measured 24 hours after coronary artery occlusion and serial serum CPK determina-

tions were performed hourly following coronary artery occlusion, the agreement between estimated myocardial CPK released and actual myocardial CPK depression was within one percent. Furthermore, when isoproterenol was administered following coronary artery occlusion, a distinct alteration in the serum CPK disappearance curve was consistently seen. The augmented myocardial necrosis occurring following this intervention was reflected both in the extent of myocardial CPK depression and the characteristic and quantitative alterations in serum CPK activity in the same animal. Studies are in progress to characterize the kinetics of serum CPK activity in man to provide a basis for the use of serial serum CPK determinations in patients with myocardial infarction. By defining the kinetics of human serum CPK appearance and disappearance, and based on the excellent correlations between behavior of serum CPK and myocardial CPK depression in animals, it should soon be possible to determine accurately the extent of myocardial necrosis in patients by means of serial changes in serum CPK activity.

DR. E. BRAUNWALD: It is difficult to exaggerate the importance of finding a method for the measurement of infarct size in patients with coronary artery disease. So many of our therapeutic interventions—such as anticoagulants, pressor drugs, inotropic agents and the application of circulatory assist devices—are evaluated by the effect they exert on mortality. We must also know, however, what effect any given intervention exerts on the total quantity of infarcted tissue. As Dr. Maroko has demonstrated, in certain circumstances the price for improving myocardial contractility may be extension of infarction. On the other hand, we now have enough leads from animal experiments that beta adrenergic blockade, balloon counterpulsation and glucocorticoid-insulin-potassium infusion may reduce infarct size, and it behooves us to extend these studies to patients in whom determination of the extent of myocardial necrosis will be critical.

Any discussion of newer developments in the treatment of myocardial infarction would be incomplete without a consideration of the contributions of surgical therapy, which will now be presented by Dr. Nina S. Braunwald.

DR. N. S. BRAUNWALD: \* As a result of continued improvements in techniques of cardiopulmonary

\*Associate Professor of Surgery.

by-pass and anesthetic management, operations on many patients who have sustained serious complications secondary to a myocardial infarction can now be carried out at an acceptable operative risk with the expectation of satisfactory clinical improvement. The complications most often requiring surgical intervention include mitral regurgitation secondary to rupture of chordae tendinae or papillary muscles, rupture of the interventricular septum, the development of pump failure secondary to ventricular aneurysm or large areas of akinesis and heart block.

**R**upture of an entire left ventricular papillary muscle or of one of the heads of a papillary muscle has been one of the most dreaded complications following acute myocardial infarction. If the resultant mitral regurgitation is very severe, or if a moderate degree of mitral reflux is superimposed on severely impaired left ventricular function, the outcome may be fatal in a matter of hours or days despite intensive medical management. On the other hand, patients in whom the hemodynamic burden imposed by the presence of the lesion is less severe and in whom the infarct is not so large as to compromise left ventricular function seriously, may survive for several months, but congestive heart failure then may develop. Our experience with mitral valve replacement in a group of patients with severe pulmonary hypertension and grossly elevated left atrial mean pressure secondary to ruptured papillary muscles has been most promising. All patients survived valve replacement and derived distinct symptomatic and hemodynamic improvement from the operation.<sup>34</sup> Whenever possible, operation is delayed until two months after the acute episode. However, if it is not possible to stabilize the patient's condition and if the clinical condition deteriorates despite intensive conservative treatment, diagnostic cardiac catheterization and early operation may become necessary, albeit at a higher risk.

A patient with this complication of myocardial infarction whom we recently treated illustrates some of the potential opportunities for clinical benefit resulting from what even a short time ago might have been considered to be aggressive therapy. The patient, a 49-year-old white man, experienced documented acute myocardial infarctions in 1965, 1969 and 1970. Following the last episode, he showed progressive decrease in

exercise tolerance, developed orthopnea, and became dyspneic at rest despite intensive medical treatment. Cardiac catheterization revealed a mean pulmonary artery wedge pressure of 28 mm of mercury, a v wave peak of 54 mm of mercury and an elevated left ventricular end-diastolic pressure (30 mm). On cineangiocardiology the left ventricle was seen to be dilated and there was diffuse poor contractility, but no localized area of wall-motion abnormality; pronounced mitral regurgitation occurred over the entire mitral orifice. Coronary angiography revealed severe occlusive disease of the proximal right coronary artery with complete occlusion of the right coronary artery in its midportion; the distal right coronary artery and the posterior descending artery filled via collaterals from the left circumflex coronary artery; there was 90 percent obstruction of the latter immediately distal to its origin, with a 75 percent occlusion of the proximal left anterior descending coronary artery. Distal vessels beyond the area of proximal occlusion appeared relatively normal.

At operation the mitral valve was replaced with a fabric-covered, ball-valve.\* Saphenous vein coronary artery by-pass grafts were placed from the aorta to the left anterior descending and circumflex coronary arteries beyond the major obstructions. Postoperatively the patient has shown progressive clinical improvement, with pronounced diminution of his symptoms of diminished cardiac reserve. Thus, in addition to relieving the severe valvular regurgitation, operation also greatly improved myocardial perfusion. Whenever feasible it appears desirable to by-pass coronary obstructive lesions and thereby, perhaps, to diminish the risk of future infarcts and improve left ventricular function while reducing the hemodynamic burden imposed by the regurgitant valve.

Resection of infarcted tissue, particularly ventricular aneurysms, is one of the most promising areas of surgical treatment of myocardial infarction. Intractable heart failure remains the primary indication for operative intervention in patients with this complication; however, persistent arrhythmias, most frequently recurrent attacks of ventricular tachycardia unresponsive to antiarrhythmic drugs, provide an additional reason for recommending operation. Approximately half of the patients with chronic ventricular aneurysms

\*Manufactured by Cutter Laboratories, Berkeley, California.



are found to have a clot lining the inner surface of the aneurysm, and this is removed routinely at the time of resection. Surgical treatment includes excision of the entire ventricular aneurysm, utilizing cardiopulmonary by-pass. A rim of scar tissue is often left to secure the sutures which are additionally reinforced with Teflon<sup>®</sup> pledgets. Whenever possible—unless the congestive heart failure is intractable and life-threatening—the operation should be deferred for six months after the most recent infarction to allow for demarcation between infarcted and healthy myocardium. The overall hospital mortality in one series<sup>35</sup> was 13 percent, and 41 of 49 surviving patients were free of symptoms postoperatively. Encouraged by the feasibility of resecting left ventricular aneurysms, more recently attempts have been made to improve left ventricular performance in patients without frank aneurysms but with large akinetic areas of myocardium demonstrated angiographically.

The limited experience in the surgical treatment of post-infarction heart failure by resecting such non-functioning areas of the left ventricular wall has been quite promising. Postoperative physiologic studies in patients has confirmed that this procedure can be expected to reduce left ventricular and diastolic volume and pressure. These physiologic changes have been associated with symptomatic improvement, suggesting that further application of this form of treatment appears warranted.<sup>36,37</sup> Obviously, if the akinetic portion constitutes a large fraction of the total ventricle, its total resection might leave a left ventricular chamber which is too small for normal left ventricular function. However, excellent results can be expected when the area of poorly functioning myocardium comprises less than 25 percent of the total ventricle.

A natural extension of resection of akinetic or aneurysmal areas of the myocardium some months or years after infarction is acute infarctectomy.<sup>38</sup> The obvious disadvantages include the hazard of suturing friable, freshly necrotic tissue, as well as the unstable and critical condition of patients considered for this type of procedure. Indeed, a number of patients have succumbed while preparations for open-heart operation were being made. On the other hand, the application at the time of operation of an epicardial mapping technique, such as that described by Dr. Maroko earlier in

this conference, should aid in defining the area requiring resection. Also, the early use of improved and more effective circulatory assist devices may help to stabilize the patient's condition and sustain the function of the remaining myocardium and of the other vital organs until operation can be carried out.

Coronary revascularization by means of saphenous vein by-pass grafts is one of the most exciting recent developments in cardiac surgery. Early experience with this procedure in the treatment of patients with severe angina pectoris and with obstructive lesions demonstrated in one or more of the major branches of the coronary arteries, seems most promising, and we have already made reference to it in connection with relief of mitral regurgitation. In patients in whom left ventricular contractility is not unduly impaired, the operative mortality for single and multiple by-pass procedures is less than 10 percent, the early patency rate for the grafts is in the range of 80 percent and the relief of angina pectoris is excellent. As many as 70 to 80 percent of symptomatic patients subjected to coronary cineangiography have been considered as good candidates for such revascularization procedures. Attempts are now being made to extend the indications for this procedure to patients with pre-infarction angina, in an effort to prevent the development of a massive acute myocardial infarction. Recently we have had favorable experience with this approach in two patients and the presentation of one of these cases illustrates the potential value of this method of treatment.

The patient, a 51-year-old man, had a diaphragmatic myocardial infarction in December 1969. He did well until two weeks before admission when he was awakened with acute anterior pressing chest pain which lasted one and one-half hours. The electrocardiogram showed an old diaphragmatic myocardial infarction and ST segment depressions and T wave inversions in the anterior precordial leads, which subsequently reverted toward normal. He did well on bed rest until the day before admission to our hospital, when he again experienced acute chest pain associated with the redevelopment of ST-T wave changes in the anterior precordial leads. Physical examination revealed sinus rhythm, a protodiastolic gallop sound, no evidence of heart failure and was otherwise unremarkable. The vital signs were normal. The electrocardiogram revealed normal sinus

rhythm with evidence of an old diaphragmatic infarction with ST segment elevations in leads 2,3, and AVF. T waves were biphasic in v2 through v4. He had mild elevation of the serum transaminase (63U) and of the creatine phosphokinase (395 I.U.). He was immediately taken to the cardiac catheterization laboratory where his left ventricular pressure was found to be 136/13 mm of mercury, and the left ventricular end-diastolic volume was normal (89 ml per square meter). However, the ejection fraction was reduced, 0.36 (normal = 0.67). There was generally diminished contractility of the entire left ventricle and areas of hypokinesis high along the anterior wall as well as at the cardiac apex. Coronary angiography revealed that there was a right dominant circulation with complete occlusion of the right coronary artery at its origin. Beyond the obstruction the distal right coronary artery filled from the left system, and gave off a large posterior descending coronary artery. There was almost complete occlusion of the proximal left anterior descending coronary artery and beading distal to the obstruction. There was minimal plaquing at the origin of the circumflex coronary artery.

It was felt that the myocardial infarction was in the process of extending and the patient was taken to the operating room in emergency immediately following the catheterization. A double saphenous vein coronary artery by-pass procedure was carried out; one graft was brought down to the right coronary artery distal to the obstruction and the other to the left anterior descending coronary artery. Measurements of blood flow through the grafts with an electromagnetic flowmeter at the operating table revealed 160 ml per minute through the former and 80 ml per minute through the latter. Postoperatively the patient required assisted ventilation for several days but showed progressive clinical improvement thereafter and was doing well at the time of discharge from the hospital, without further pain of myocardial ischemia or development of further electrocardiographic changes suggesting transmural infarction.

Rupture of the ventricular septum is one of the less common complications of acute myocardial infarction requiring surgical intervention. The time interval between the infarction and the rupture most commonly ranges from four to twelve days and two-thirds of the patients who

have this complication die within two weeks. Surgical closure of the defect is indicated when the patient shows evidence of progressive deterioration and intractable pump failure with pulmonary edema or cardiogenic shock or both.<sup>39,40</sup> The diagnosis should be confirmed by cardiac catheterization before operation. One patient with this complication recently treated at the University Hospital of San Diego County, who required emergency surgical treatment to correct the hemodynamic burden created by the presence of the lesion illustrated many aspects of this challenging clinical problem.

The patient was a 53-year-old white man who was transferred to our institution three weeks after onset of his first myocardial infarction. The initial episode had been associated with severe substernal chest pain, diaphoresis and shortness of breath, but the early course was uneventful. On the third day following the onset of symptoms, the patient suddenly became cold, clammy and hypotensive, and rales were noted at both lung bases. On the following day atrial flutter developed, and a loud high-pitched apical systolic murmur appeared. During the subsequent 17 days the patient evidenced progressive confusion, congestive heart failure and hypotension, requiring intravenous norepinephrine to maintain an adequate arterial pressure. At the time of admission the patient was confused, pale, and lethargic. There was evidence of both left and right ventricular enlargement and a systolic thrill was palpable along the lower left sternal border. There was a grade IV/VI high-pitched holosystolic murmur at the apex and along the lower left sternal border. There were rales over both lung bases posteriorly. The liver was enlarged 6 cm below the right costal margin and the jugular venous pulse showed decided increase in pressure. On a film of the chest the pulmonary vasculature was congested and diffuse cardiomegaly was present. The electrocardiograms showed nodal rhythm with changes of an anteroseptal infarct. The serum creatinine was 2.8 mg per 100 ml and the blood urea nitrogen 140 mg per 100 ml. Right heart catheterization revealed a significant left-to-right shunt at the ventricular level with a pulmonary/systemic flow ratio of 5:1. The pulmonary artery pressure was elevated to 66/20 mm of mercury. In view of the patient's precarious condition, despite what was considered to be intensive medical treatment, he was



taken to the operating room on the day following catheterization and a large (3x3.5 cm) ventricular septal defect with greyish friable margins was evident in the lower portion of the septum near the apex. It was repaired with a Teflon fabric patch and with sutures reinforced with Teflon felt pledgets. A large (5x6 cm), thinned out, poorly contracting area of muscle was present on the anterior wall of the left ventricle following the closure of the defect. Since this muscle did not appear to be contributing to effective cardiac contraction it was imbricated with a series of heavy silk sutures with Teflon felt pledgets, thereby excluding the akinetic area from the rest of the left ventricle. Cardiopulmonary by-pass was discontinued without difficulty. Tracheostomy was carried out and support of assisted ventilation was needed for a time, but otherwise the patient made uneventful recovery. He was able to take long walks and was otherwise asymptomatic when last seen as an outpatient.

This patient illustrates that corrective operation in many patients suffering from the complications of an acute myocardial infarction may be life-saving. Operative intervention is indicated when intensive medical management has not been effective. As our experience with these patients increases, it seems probable that operative treatment will be considered before irreversible deterioration in the function of the surviving myocardium and of the other vital organs has occurred.

DR. E. BRAUNWALD: The problems posed by acute myocardial infarction are both extremely serious and enormously complex. In this conference we have reviewed just a few of the current research efforts designed to attack this problem. It is becoming evident that no simple therapeutic "magic bullet" is likely to provide a solution. Instead, it is more likely that in the foreseeable future investigators will continue to chip away at various aspects of this condition. In addition to some of the areas touched on in this conference, important advances in the prevention and treatment of acute myocardial infarction are likely to come from advances in lipoprotein chemistry, the genetics of lipid disorders, the clinical pharmacology of lipid-lowering agents, public education campaigns designed to encourage the patient with an infarct to seek immediate medical attention, the detection and early treatment and hos-

pitalization of patients with a fresh infarct and the appropriate application of circulatory assist devices to the patient with early pump failure.

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## IS IT FAT OR CUSHING'S DISEASE?

"The one definitive way of diagnosing Cushing's disease, as opposed to obesity, is to follow the level of free cortisol, which gets into the urine and is excreted like creatinine. . . .

"Levels of cortisol are not constant throughout the day, except in Cushing's disease. In a normal person both ACTH and cortisol vary. About two o'clock in the morning . . . , there's a huge spurt of ACTH and cortisol. Then during the day they fall off to a low level about 10 o'clock at night—that is, if there are no stresses. This diurnal variation results in a difference in plasma cortisol of about 50 percent. In other words the peak at about eight o'clock in the morning is about twice as high as the midafternoon levels. This lends itself to survey—if cortisol is constant all the time in Cushing's disease, one ought to be able to pick that up.

"[In our practice] we ask the patient to take two dexamethasone pills, 1 or 1.5 mg, at 11 p.m. If the patient is just fat, ACTH output from the pituitary will be immediately inhibited. The level of cortisol in the blood will fall and there will be no replenishment for the next four hours. ACTH and cortisol have been inhibited. As a result, levels of cortisol in the blood are very low the next morning. If the patient has Cushing's disease, ACTH and cortisol cannot be inhibited and the level remains constant and is still high the next morning.

"There is an occasional error when a patient is terribly excited and hates to be 'stuck.' As soon as you stick him at eight o'clock in the morning to take the blood sample of plasma, his cortisol level rises tremendously. If you wait a while before making a second attempt, you might have high levels, even in normal people. But if you've given the patient a good sleeping pill the night before, and you obtain the cortisol-containing plasma easily, then the levels in normal people (including fat people) should be down, whereas the level in Cushing's patients is always elevated; and that makes the diagnosis."

—PETER H. FORSHAM, M.D., San Francisco  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Reactive Hypoglycemia

## Mechanisms and Management

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SLEISINGER:\* Grand Rounds today involves an interesting disorder of carbohydrate homeostasis—hypoglycemia. The patient with this syndrome will be presented by Dr. Norman Coleman.

DR. COLEMAN:† A 26-year-old Caucasian woman was admitted to the hospital with a six-year history of headaches which had increased in frequency over the nine months before admission. Although they lasted several days each time, the headaches were never severe enough to cause her to stay home from work. They commenced in the neck, progressed to the side of the head and were not relieved by aspirin. Associated symptoms included sleepiness, slurred speech, chills, tremulousness, occasional diaphoresis and nausea, but no vomiting. The symptoms were unrelated to menses. There was no history of scotomata, loss of consciousness, seizures or other neurological symptoms during these episodes. There was no clear relationship to meals, although food did help the headaches. Past medical history included some nervousness which had been treated with chlorthalidone hydrochloride (Librium®). The patient had been taking norethindrone with mestranol (Orthonovum®) birth control pills for the past year. A 32-year-old sister had a history of headaches and hypoglycemia documented by glu-

cose tolerance test. There was no known family history of diabetes.

Results of physical examination, including neurological testing, were entirely within normal limits. The blood pressure was 120/70 mm of mercury and the pulse regular at 76 beats per minute. Hemoglobin was 12.4 grams per 100 ml and leukocytes numbered 4,900 per cu mm with normal differential. Results of urinalysis, electrocardiogram, x-ray films of chest and skull, and an electroencephalogram were all within normal limits. A 24-hour urine measurement of 17-hydroxy- and 17-ketosteroid excretion was normal. A morning plasma cortisol level was 44 micrograms per 100 ml, while an early afternoon level the same day was 17 micrograms per 100 ml. Dexamethasone (2 mg) was administered at 11 p.m. the same day, and the plasma cortisol level was 4.5 mg per 100 ml on the following morning. The elevated plasma cortisol was considered compatible with the history of oral contraceptive therapy, since the pituitary-adrenal axis showed normal suppression. The oral glucose tolerance test showed the following results:

Time (hours)	0	½	1	1½	2	3	4	5
Plasma glucose (mg per 100 ml)	92	200	210	140	100	52	70	75

At the third and fourth hour periods of the glu-

\*Marvin H. Sleisenger, M.D., Professor of Medicine.

†Norman C. Coleman, M.D., Assistant Resident in Medicine.

cose tolerance test the patient complained of headache similar to that she had experienced in the past. Reactive hypoglycemia was diagnosed and the patient was discharged with prescription of a high protein, low carbohydrate diet. On this dietary regime she has been asymptomatic for the two months since discharge from the hospital.

DR. SLEISINGER: This patient with hypoglycemia presents a difficult problem in diagnosis and treatment. Dr. John Karam will discuss some of these aspects.

DR. KARAM: \* Patients who have rather nonspecific complaints and no abnormalities on physical examination are always a difficult management problem. A succession of normal laboratory tests usually confirms the initial impression that organic disease is not present, and the symptoms are then attributed to the tensions of modern living. Usually the only form of therapy given is reassurance, and since it does not often succeed the patient often consults a number of physicians and tries a succession of tranquilizers without benefit. Inevitably the question of hypoglycemia is raised, frequently by the patients themselves owing to wide publicity in the lay press. "Health food" store shelves are lined with current books paraphrasing the original classic, *Body, Mind, and Sugar*,<sup>1</sup> which emphasizes an almost mystical role of low blood sugar in many of the physical ills of our times. This book, written in 1951 and unrevised since the original publication, has been reprinted almost every year and remains a best seller. The authors of this book are a physician, E. M. Abrahamson, and one of his patients, A. W. Pezet, who had multiple complaints including nervousness, weakness, and fatigue which persisted despite attempts at management by numerous physicians. It was only after Dr. Abrahamson performed a glucose tolerance test and demonstrated a reduced blood sugar at three to four hours that successful therapy was begun. This therapy consisted of frequent, small feedings of a low carbohydrate, high protein diet. With the help of his patient, who was a professional journalist, Dr. Abrahamson wrote a very entertaining and expressive story of the dramatic results obtained in this and other cases.

The first half of the book gave an excellent and remarkably accurate scientific description of carbohydrate homeostasis with emphasis on the role of insulin in its regulation and the hazards of hy-

perinsulinism. While most readers in the scientific community would accept that Mr. Pezet's weakness, nervousness and fatigue could have been explained by the reactive hypoglycemia, it was more difficult to accept the second half of the book wherein the cure of his asthma, hay fever and allergies, as well as the cure of peptic ulcers, rheumatic fever and arthritis in other patients, was attributed to stabilization of the blood sugar level. Nevertheless, the book remains quite popular, despite its shortcomings, and a foundation located in New York distributes it nationally to its members who suffer in common from hypoglycemia.

In the patient presented today the obvious question is whether the headaches, nervousness and other nonspecific symptoms had any correlation with the documented measurement of a plasma sugar level of 52 mg per 100 ml recorded three hours after 100 grams of glucose was administered orally. Many physicians do not consider a blood glucose level above 40 mg per 100 ml or a plasma glucose above 46 mg per 100 ml to be low enough to cause hypoglycemic symptoms. In one study, continuous automatic monitoring of blood glucose demonstrated that nine out of twelve asymptomatic subjects had a blood glucose between 44 and 58 mg per 100 ml at some time during an oral glucose tolerance test.<sup>2</sup> However, the glucose response of the present patient must be considered in context with the clinical problem. The general pattern of the oral glucose tolerance test was abnormal, with initial hyperglycemia (200 mg per 100 ml in the first half hour) and a relatively rapid fall in plasma glucose to 52 mg per 100 ml by three hours. As continuous monitoring was unavailable, we cannot ascertain the exact minimal level to which plasma glucose may have fallen in this patient. The development of her chief complaint, headache, at the time of the lowest measured plasma sugar level and her own observation that food often relieved her headaches were additional points suggesting an etiological relationship between symptoms and blood glucose levels.

The pattern of response to the oral glucose tolerance test is a great help in classifying patients with hypoglycemia.<sup>3</sup> The presence of a "reactive" rather than a "fasting" hypoglycemia in this patient makes it unlikely that the diagnosis is the result either of autonomous production of insulin by an insulinoma or of heterogenous factors involved in the hypoglycemia related to nonpancreatic tumors.

\* John H. Karam, M.D., Assistant Professor of Medicine.



## REACTIVE HYPERINSULINISM

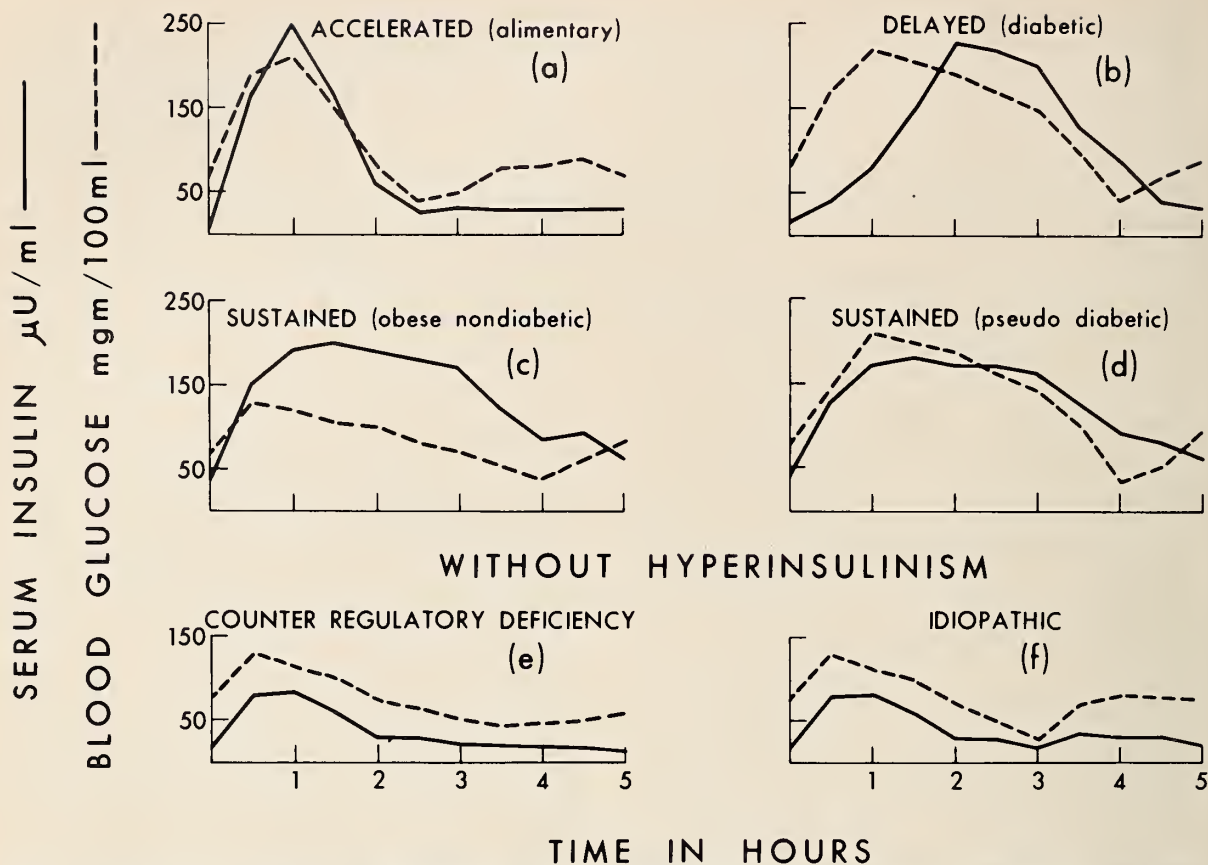


Chart 1.—Patterns of Reactive Hypoglycemia: Reactive hypoglycemia with reactive hyperinsulinism (a,b,c,d). Reactive hypoglycemia with normal insulin response (e,f). The abscissa records time after ingestion of 100 gm of glucose.

### Classification of Reactive Hypoglycemia

With the establishment of a "reactive" type of hypoglycemia by clinical history, as well as by plasma glucose measurements, it is then useful to determine whether the pattern of response to the oral glucose load is one of "early" or "late" hypoglycemia. A typical "early" hypoglycemia occurs within three hours of the ingestion of glucose, whereas "late" hypoglycemia occurs three to five hours after receiving the glucose. The pathogenetic mechanisms and management of these responses are quite different.

**"Early" Hypoglycemia.** The present patient demonstrated a pattern of glucose response in the first hour that is characteristic of the alimentary type (Chart 1,a). There was an exaggerated rise of the ascending limb of the curve to reach supra-normal values within 30 minutes, followed by a rapid descent associated with symptoms. Al-

TABLE 1.—Classification of Reactive Hypoglycemia

#### "Early" Hypoglycemia

Postgastrectomy  
Increased vagal tone

#### "Late" Hypoglycemia

Diabetic reactive hypoglycemia  
Nondiabetic "late" hypoglycemia  
Obesity  
Pseudodiabetes  
Counter regulatory deficiency  
Idiopathic reactive hypoglycemia

though serum insulin levels were not measured in this patient, they almost invariably reach very high levels in the first hour when associated with this particular type of plasma glucose response. "Early" hypoglycemia is quite common in postgastrectomy cases<sup>4</sup> but may also occur in other patients, especially in thin, nervous, compulsive,

hyperactive persons who often complain of gastrointestinal difficulties compatible with increased vagal tone.

The pathogenesis of this pattern of response consists of at least two components: accelerated rate of glucose absorption and intestinal betacytotropic factors.

*Accelerated Glucose Absorption.* The most obvious cause of accelerated glucose absorption is an abnormally rapid absorption of the alimentary glucose in patients who have had gastrectomy, as well as in those who simply have accelerated gastric emptying, possibly owing to increased vagal tone. Hyperinsulinism, resulting from the initial hyperglycemia, as well as from the increased vagal effect on pancreatic beta cell secretion, produces hypoglycemia.

*Intestinal Betacytotropic Factors.* It has been clearly demonstrated that the hyperinsulinism which is observed in patients who have had gastrectomy cannot be the result of only the accelerated rate of glucose absorption, since similar hyperinsulinism does not develop when glucose is infused rapidly to produce comparable levels of hyperglycemia.<sup>4</sup> This finding, that the insulin response depends on the route of glucose administration rather than on the circulating glucose level alone, was a very exciting development in the understanding of insulin secretion and its control. It had long been known that a given amount of glucose produced higher blood glucose levels when administered intravenously than when ingested. The assumption was that when glucose was administered orally the time necessary for gastrointestinal absorption and removal by the liver before reaching the systemic circulation accounted for the lower levels. If this were the case, then the higher glucose concentration in the pancreatic artery after intravenous administration would have been expected to produce higher levels of circulating insulin than did glucose by mouth. However, when techniques were developed to measure insulin, it was surprisingly reported that oral glucose produced much higher insulin levels than did comparable intravenous doses.<sup>5</sup> This finding suggested that insulin release was not dependent on blood glucose levels alone and that something produced during alimentation was enhancing the stimulatory effect of glucose on insulin release.

Table 2 relates the historical sequence<sup>5</sup> in the development of the concept that betacytotropic

TABLE 2.—*Historical Sequence of Development<sup>5</sup> of Concept that Betacytotropic Factors Are Present in Normal Persons*

1904	Secretin Induced B-Cell Hyperplasia
1923	Secretin Reduced Blood Sugar in Dogs
1940	Hypoglycemic Effect of Secretin Not Confirmed
1964	Oral Glucose Increases Insulin Levels More Than IV Glucose
1966	Extracts of Duodenum Increased Blood Insulin Level, as did the following: Secretin Pancreozymin Gastrin Glucagon-Like Substance

factors are present in normal subjects. In 1904 it was reported that secretin administration produced beta cell hyperplasia. This finding was overlooked until after the discovery of insulin, at which time it was reported that secretin also reduced the blood glucose of dogs. However, when improved micromethods were developed for measuring blood glucose, it was observed and subsequently confirmed that there was no real hypoglycemic effect of secretin in dogs.<sup>5</sup> Thus, for a time the concept of a role of secretin as a betacytotropic substance was discarded. Only after insulin measurements demonstrated the superior insulinotropic effect of oral as compared with intravenous glucose was the problem reinvestigated.

When extracted duodenal mucosa was shown to stimulate insulin release<sup>6</sup> the term "gut factor" became widely used, and its chemical isolation, purification, and characterization were expected momentarily. The early reports of secretin-induced beta cell hyperplasia seemed to be vindicated when secretin was shown to stimulate insulin secretion both *in vivo* and *in vitro*, despite its verified lack of hypoglycemic effect in animals. However, investigators were dismayed when instead of finding a single betacytotropic factor, they found that just about every gastrointestinal hormone tested had insulinotropic properties.<sup>7</sup> Unger<sup>8</sup> reported finding a variety of different peptides with glucagon-like immunoreactivity in gastrointestinal mucosa; these peptides can enhance insulin release. Other known insulin secretagogues found in gastrointestinal mucosa include gastrin and cholecystokinin-pancreozymin.<sup>7</sup> The question of the nature of this gut factor is still unresolved. It is not clear whether all of these enteric hormones participate in the enhancement of insulin release by some common mechanism such as cyclic-AMP (Adenosine 3' 5' monophosphate) generation, or whether, as Creutzfeld<sup>7</sup>



speculates, the available data represents pharmacological observations; and the actual physiological betacytotropic hormone remains as yet undetected.

Regardless of its nature, an enteric insulino-tropic factor certainly seems to exist and may well be produced excessively in postgastrectomy patients and other persons in whom gastric contents empty at an accelerated rate. An increase in glucagon-like immunoreactivity after oral glucose has been reported recently in two patients with reactive hypoglycemia and has been suggested as a pathogenetic factor in their hypoglycemia.<sup>9</sup>

*"Late" Hypoglycemia.* Diabetic reactive hypoglycemia (Chart 1,b) was first described in 1956 by Seltzer et al<sup>10</sup> in a classic study of 110 patients with normal fasting blood sugar but impaired carbohydrate tolerance. Hyperglycemia persisted for as long as two to three hours after ingestion of glucose, but then was followed by a transient fall to hypoglycemic levels between the third and fifth hour.

In contrast to hyperactive patients with "early" hypoglycemia, patients with "late" hypoglycemia tend to be more phlegmatic, with a high incidence of obesity, and frequently have a positive family history of diabetes mellitus. Serum insulin response to glucose is delayed initially in patients with early adult-onset diabetes, accounting for their carbohydrate intolerance, but gradually rises so that by the second and third hour of the glucose tolerance test hyperinsulinism occurs.<sup>11</sup> Thus, the pathogenesis of this type of "late" hypoglycemia is believed to be within the beta cell itself, and it is thought to represent one of the earlier manifestations of diabetes mellitus.

Nondiabetic "late" hypoglycemia has been described in obese patients who have an early and sustained release of insulin in association with peripheral insulin antagonism (Chart 1,c). This peripheral antagonism has been variously ascribed to abnormally enlarged adipose cells, intramuscular inhibition of glucose metabolism by raised fatty acids, or a combination of these and other, as yet unknown, antagonists. Whatever the cause, this peripheral antagonism to insulin's action results in a delayed postprandial clearance of circulating glucose, although an abnormal elevation of blood glucose does not occur. The prolongation of glucose clearance may stimulate the beta cells and, in addition to the excessive ingestion of calories with their consequent release of beta-

cytropic factors, contribute to the well-documented islet cell hyperplasia and sustained hyperinsulinism found in most obese persons.<sup>12</sup> When islet cell hyperplasia progresses so that the postprandial hyperinsulinism overcompensates for the peripheral antagonism, "late" hypoglycemia occurs.

Nondiabetic "late" hypoglycemia has also been described in patients who have been referred to as having pseudodiabetes (Chart 1,d). These patients have an early and sustained hypersecretion of insulin in association with both an abnormal elevation and a delayed clearance of glucose. In these patients mild carbohydrate intolerance occurs during the initial two or three hours of a glucose tolerance test, and then a "late" hypoglycemia occurs at four or five hours. The presence of a normal or, more often, a supranormal early phase of insulin release differentiates these patients from those with "true" diabetes mellitus. In pseudodiabetes an early release of insulin occurs in response to glucose ingestion. An end organ resistance to the action of these high levels of circulating insulin, however, provides the best explanation for the abnormally elevated blood glucose levels during the first hour of the glucose tolerance test.

In a series of 238 obese subjects reported upon by Faludi et al,<sup>13</sup> 101 had "late" hypoglycemia four hours after a glucose tolerance test. Of these, 27 had normal carbohydrate tolerance in the first three hours, while 74 showed minimal hyperglycemia during this time. Although measurement of early insulin release was not reported in this study, it is our experience that the majority of obese subjects with normal fasting blood glucose and only minimally impaired carbohydrate intolerance would have a supranormal initial release of insulin after glucose and could be termed as having "pseudodiabetes."<sup>12</sup>

Certain regulatory mechanisms are normally available to counteract any excessive hypoglycemic effect of insulin during the latter part of a glucose tolerance test (Chart 1,e). These include pancreatic glucagon, catecholamines, growth hormone, sympathetic nervous stimulation, and cortisol. Deficiency in release of these substances in response to hypoglycemia may thus lead to more pronounced and sustained hypoglycemia.

In the presence of normal glucose tolerance and normal insulin release over the first two hours, patients with reactive hypoglycemia should

first of all be carefully evaluated for deficiencies, of the counter regulators. In the absence of these deficiencies, such cases have been classified as idiopathic reactive hypoglycemia (Figure 1,f).

## Diagnosis and Treatment of Reactive Hypoglycemia

In patients without fasting hypoglycemia who have vague autonomic symptoms temporally related to meals, diagnosis is best established by a five-hour oral glucose tolerance test. This test is preferably supervised by a physician so that, in addition to regular blood sampling every 30 minutes, he can obtain a blood sugar determination at the first sign of symptoms, lest a transient period of hypoglycemia be missed.

Treatment is based on the pattern of reactive hypoglycemia obtained. The measurement of serum insulin and blood sugar better delineates the physiological disturbance as shown in Chart 1. In our laboratory, fasting levels of insulin seldom are above 30  $\mu$ U per ml in normal persons but may be as high as 50  $\mu$ U per ml in obese persons. After a glucose load, the normal person usually does not have an increase in serum insulin level above 100  $\mu$ U per ml during his peak insulin response between 30 and 60 minutes.

In an accelerated hyperinsulinism with early hypoglycemia (Chart 1,a) treatment is aimed at reducing the large quantity of food suddenly being presented to the small intestine after meals in patients who have had gastrectomy or those with increased vagal tone, in order to reduce rapid excursions of blood glucose. The patient is offered small, frequent, high protein feedings which contain no processed sugar and only limited carbohydrate. Anti-cholinergic drugs have also been used to inhibit vagal tone and delay gastric emptying. In a well studied case, such cholinergic blockade reduced the rate of gastric emptying, normalized the exaggerated hyperinsulinism and corrected the "early" hypoglycemia.<sup>14</sup> Certain pharmacological agents, including diazoxide,<sup>14</sup> mannoheptulose,<sup>15</sup> and diphenylhydantoin sodium (Dilantin®),<sup>16</sup> may induce hyperglycemia in man with a reduction in serum insulin levels. While these agents offer possible therapeutic approaches in this and other types of reactive hypoglycemia, they as yet have not received adequate clinical trials.

Delayed hyperinsulinism with "late" hypoglycemia (Chart 1,b) is the pattern of reactive hypoglycemia found in patients with diabetes mellitus. Elimination of sugar-containing foods and frequent feedings with increased proteins reduces the initial hyperglycemia that precipitates the delayed hyperinsulinism. Also, in this situation restoring the early phase of insulin release with tolbutamide<sup>17</sup> administration has been reported to be clinically useful.<sup>18</sup>

In sustained hyperinsulinism associated with obesity and pseudodiabetes (Chart 1,e and d) caloric intake is lowered to reduce the obesity and interrupt the cycle producing islet cell hyperplasia and consequent hyperinsulinism. Small, spaced feedings low in carbohydrate, free of sugar and increased in protein are also beneficial. In addition, phenformin hydrochloride (DBI®) has proved to be effective in a large group of obese patients by abolishing late hypoglycemia following a glucose load.<sup>13</sup> The mechanism of action involved with the administration of phenformin may be a reduction in the rate of absorption of ingested glucose by the intestinal mucosa, which results in a smaller elevation of blood glucose and consequently decreased insulin production by the hyperplastic pancreatic beta cells.

Specific replacement therapy is difficult in most counter regulatory deficiencies, except in the case of cortisol insufficiency. Thus, reliance on multiple, small, spaced feedings to minimize increases in blood sugar and insulin secretion would be recommended for these patients as well as for those with idiopathic reactive hypoglycemia.

It is of interest that most patients in all the categories of reactive hypoglycemia seem to respond to a substitution of protein for carbohydrate in their diet even though protein ingestion results in insulin release. It has been suggested that the concomitant production of glucagon offsets the action of this insulin.<sup>19</sup>

In summary, the patient discussed today, who is not obese, has a glucose pattern suggestive of alimentary hypoglycemia with an exaggerated early rise and then a return to normal and finally hypoglycemic levels. The Orthonovum® therapy may have produced just enough insulin antagonism to slightly delay the hypoglycemia in this patient from the 120 to 150 minutes normally seen in the more classical cases of alimentary hypoglycemia. Unfortunately, insulin measurements were not undertaken to confirm the impression of accel-



erated hyperinsulinism. Her clinical picture is, however, typical enough to suggest a trial of low carbohydrate, high protein diet of small, spaced feedings. Since the hypoglycemia and symptoms are rather mild, this therapy should be adequate, with anticholinergic agents kept in reserve in case symptoms become more severe. Phenformin might also be of use in alimentary hypoglycemia, since it reduces the rate of glucose absorption.

DR. HAVEL:\* How frequently do atypical symptoms, such as headache, occur? Since the glucose tolerance test alone is not very reliable as a diagnostic aid, and not everybody can measure insulin levels, how much do you rely on the history in evaluating the nature of the disorder?

DR. KARAM: This question is difficult to answer. As physicians we were taught that if a person's blood sugar drops from a high level to a low level, we could expect certain autonomic symptoms attributed to epinephrine. In *Body, Mind, and Sugar*, the authors describe the usual responses, but claim that many atypical symptoms can also occur. They describe, for instance, the pitcher in the baseball game who had perfect control until the eighth inning, when he suddenly blew up and walked everybody. They also imply that most husbands who argue with their wives before supertime are "hypoglycemic," and if only their eating habits were altered their marriage would be blissful. Without documentation of blood glucose levels, it is hard to prove (or disprove) whether these are symptoms of hypoglycemia. However, I would say that I believe atypical symptoms, such as headache, can occur; but I do not know how I could be certain. I suppose we should give the patient the benefit of the doubt if we observe

atypical symptoms which occur during documented reactive hypoglycemia and are relieved by eating.

#### TRADE AND GENERIC NAMES OF DRUGS

*Librium*® ..... chlordiazepoxide hydrochloride  
*Orthonovum*® ..... norethindrone with mestranol  
*Dilantin*® ..... diphenylhydantoin sodium  
*DBI*® ..... phenformin hydrochloride

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\*Richard J. Havel, M.D., Professor of Medicine.

# Important Advances in Clinical Medicine

## *Epitomes of Progress -- Pathology*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Aldosterone Levels

The assessment of the renin-angiotensin system is usually accomplished by the measurement of plasma renin activity (PRA) by a variety of techniques. In general, these levels are elevated in secondary hyperaldosteronism. PRA measurements are those most frequently used to (1) support the diagnosis of an aldosterone-producing tumor and (2) the identification of certain types of renovascular hypertension diseases where peripheral levels and measurement of renin concentration in both renal veins will identify an abnormal kidney which may be the causative factor.

PRA levels are quite sensitive to position and sodium intake. Care must be used in the interpretation of PRA in suspects with primary aldosteronism. The PRA may be normal after marked salt restriction and standing. If the stimulus is severe enough, even the suppressed levels in this disorder

could become normal. A single peripheral PRA level provides little information, if any. In patients with essential hypertension, 20 to 30 percent may have subnormal levels.

The measurement of bilateral renal vein renin can be most useful in the identification of the abnormal kidney if the ratio (expressed as larger renin value over smaller) is greater than 1.7:1. These measurements may be of use in hypoplastic kidneys, hydronephrosis, and unilateral pyelonephritis. Its usefulness may soon warrant the use of PRA as the next logical procedure after an abnormal intravenous pyelogram.

EDWARD G. BIGLIERI, M.D.

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## Selective Deficiency of Immunoglobulin A (IgA) And Autoimmunity

A significant correlation between the occurrence of autoimmune hypersensitivity disease and selective deficiency of IgA has been established. The apparent explanation of the correlation is that IgA deficiency allows selective absorption of antigens via the gastrointestinal and respiratory tract. These antigens may provoke an immune response that exhibits cross reaction with host tissues. Antitissue antibodies are common in selective IgA deficiency as are hypersensitivity diseases such as lupus erythematosus.

ERNEST E. TUCKER, M.D.

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## Detection of Immune Complexes in Human Serum by Precipitin Reaction With C1q\* Component of Complement

Immune complexes formed by antigen-antibody reactions within the circulation can be detected by their reactivity with C1q in gel diffusion producing a precipitin line at the point of interaction. This technique should prove quite useful in the clinical diagnosis of immune complex disease.

C1q is not yet commercially available and is somewhat difficult to prepare in the laboratory, thus currently limiting application of this technique. The method has been successful in detecting immune complexes in patients with lupus

\*First component of complement.

erythematosus and in joint fluids from rheumatoid arthritis where the serum complement was low. EDTA enhances the precipitin reaction. Aggregated gamma globulin will also give this precipitin reaction.

ERNEST S. TUCKER, M.D.

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Agnello V, Winchester RJ, Kunkel HG: Precipitin reactions of the C1q component of complement with aggregated beta globulin and immune complexes in gel diffusion. *Immunology* 19:909-919, 1970

## C3\* Lytic Factor in Nephritis

A factor responsible for lowering complement levels has been identified in the serum of patients with progressive hypocomplementemic glomerulonephritis. This factor acts on complement by combining with a beta globulin cofactor to produce an enzymatic complex that degrades C3 by cleavage to smaller fragments. It is similar in many ways to a factor isolated from the venom of the cobra (*Naja naja*) which also activates a serum beta globulin to enzymatically cleave C3. None of these factors or cofactors are identifiable with complement components. The lytic factor appears to be responsible for the lower serum complement. Corticosteroid therapy of the patients with hypocomplementemic nephritis results in disappearance of the lytic factor and return of normal complement levels.

ERNEST S. TUCKER, M.D.

\*Third component of complement.

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## Diagnosis of Respiratory Distress Syndrome (Hyaline Membrane Disease) by Amniocentesis

Prevention of respiratory distress syndrome (RDS) of the newborn (hyaline membrane disease) is now possible through recent research work on the various surface active phospholipids in lungs. As fetal lungs mature lecithin appears in significant amounts in addition to the less effective, earlier appearing sphingomyelin. The ability of the lung to remain expanded after birth is directly related to the amount of lecithin present. These phospholipids can readily be found in the amniotic fluid, thus the ratio of lecithin to sphingomyelin (L:S) may be determined in a test tube thin layer chromatogram after appropriate extraction and simple purification. The relative quantities are roughly estimated measuring height and width of the spots on the developed chromatograms. If the L:S ratio is less than 1.5:1 the risk of respiratory distress syndrome is very high. If the ratio is greater than 1.8:1 the risk is very low. By waiting in elective situations until the ratio is favorable, RDS may be prevented. In the event that delivery cannot be postponed the physician is forewarned and may initiate appropriate steps before birth.

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## Mechanisms of Blood Clotting

Clotting factors can be classified into three groups: (1) thrombin-sensitive factors: viz., fibrinogen and factors V, VIII and XIII; (2) vitamin K-dependent: viz., prothrombin, factors VII, IX and X; (3) contact factors: viz., factors XI, XII and possibly the recently described Fletcher fac-

tor. The clotting sequence is triggered off by a reaction involving Hageman factor (XII); the activated Hageman factor then reacts with factor XI converting it to an active form, XIa, which in turn activates factor IX. In the presence of calcium ions the activated factor IX reacts with factor VIII and phospholipids released from platelets to form a complex which converts factor X to its activated form, Xa. The Xa in turn reacts with factor V, platelet phospholipids and calcium to form another complex which converts prothrombin to thrombin. This enzyme converts fibrinogen to fibrin monomer by splitting off two small polypeptides from the molecule and the fibrin monomer then polymerizes to form a fibrin clot. Finally the fibrin clot is rendered more stable and urea insoluble by factor XIII following its activation by thrombin. The first traces of thrombin potentiate factors V and VIII but as the thrombin level increases these factors are destroyed, clotting is decelerated and the thrombin already formed is neutralized by various antithrombins. In the presence of tissue juices the above pathway (referred to as the *intrinsic* system) is short-circuited; a protein factor and certain phospholipids in the tissue react with factor VII in the presence of calcium to activate factor X directly. The subsequent events in this, the *extrinsic* system, are the same as in the intrinsic system.

CECIL HOUGIE, M.D.

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## Practical Application of the Use of Immunofluorescence in Renal Biopsy

With the availability of the cryostat and monospecific fluorescein-labeled antisera from commercial sources, fluorescent microscopy can become part of the routine evaluation of a renal biopsy. Generally the technique is the direct method, using antisera against human IgG, complement, or fibrinogen; no consistent staining having been found with antisera against other serum proteins.



Most of the data accumulated has been from reactions seen in the glomeruli with igc antiserum, noting either a linear or a granular staining pattern. The basic assumption is that with a linear staining along the glomerular loops one has a disease process with an antibody directed against the glomerular membranes, whereas a lumpy or granular pattern suggests an immune complex disease with the complexes "caught" in the glomerulus. In Goodpasture's disease, rapid progressive glomerulonephritis, and nephropathy with burns, there may be a linear deposit of igc; while in systemic lupus erythematosus, carcinomatous nephropathy, malaria, and post-streptococcal nephritis, a granular pattern may be seen. Complement antiserum is useful because sometimes it is the only protein found in the glomerulus and from its pattern, or in conjunction with igc staining, the disease process can be better defined. Fibrinogen is found in many of the above diseases but is predominate in the renal disease associated with toxemia of pregnancy. In transplantation the linear pattern may herald problems because of an antiglomerular membrane antibody. If pyelonephritis is suspected, fluorescein-tagged antisera against bacterial antigens can be used to detect culture-negative pyelonephritis.

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#### Pituitary Hormone Assay

The concentrations of all major human anterior pituitary hormones in serum can now be determined specifically and precisely by radioimmunoassay. With few exceptions, anterior pituitary function should be evaluated directly by radioimmunoassay of hormones in serum rather than by bioassay of urinary excretory products, etc. Reagents for radioimmunoassay of luteinizing hormone, follicle stimulating hormone and growth hormone (GH) are available commercially and the

methods are being established in many clinical laboratories. Recent studies indicate that human prolactin also exists distinct from GH and radioimmunoassays have already been developed for this hormone. Human prolactin appears to be secreted primarily in late pregnancy and in association with lactation. Development of similar radioimmunoassays for low molecular weight agents related to pituitary function (steroids, prostaglandins, cyclic AMP and hypothalamic releasing factors) are progressing rapidly and should result in quantum jumps in our understanding of hormonal regulation of bodily function.

A. REES MIDGLEY, M.D.

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#### Implication of Epstein-Barr Virus in Human Disease

The Epstein-Barr virus (EBV) is a herpes-like virus initially reported by Epstein and Barr in continuous lymphoblastic cell cultures derived from Burkitt lymphomas. The observation of elevated antibody titers in patients with variable diagnoses including infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease and lymphocytic leukemia has raised the possibility that this virus may be the etiologic agent in these diseases. No direct evidence, however, has been presented to substantiate this possibility. Furthermore, serological studies have shown that the virus may be common in the general population, particularly in the low socio-economic groups.

It is postulated that after EBV infection, the virus remains inactive until another factor alters the apparent steady state of the host, and replication and antibody production then occurs. In infectious mononucleosis the EBV antibodies are demonstrated at about the same time as the heterophile antibodies and may persist indefinitely, unlike the heterophile antibody levels which

usually fall quickly. At present the value of EBV serological studies in routine diagnosis has not been clarified.

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### Computer-Based Inventory and Information Systems for Blood Banks

The availability of blood and blood products in sufficient quantities is an essential component in the delivery of health care. The regional blood bank is concerned with input of blood (donor recruitment), distribution of blood (inventory control and component preparation) and use or disposition of blood. These functions can be greatly facilitated by the application of a computer-based information system. Systems utilizing either dedicated or time-sharing computers are now available which offer: donor files with automatic call-up to actively control blood input, minimizing shortages without incurring excessive outdating; inventory programs to track the blood in the system using critical parameters such as location, ABO and Rh type, and days remaining before expiration; and a donor-patient link to simplify control of problems such as transfusion hepatitis. Statistical summaries and management reports produced by the computer provide a means to develop strategies which maximize the use of the community blood resources. It is too early to assess the cost-effectiveness of these systems, but experience indicates that the added cost will result in significant improvement in blood bank services.

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### Slow Virus Infection of Nervous Tissue

One of the most exciting advances in neuropathology was the demonstration by Gajdusek et al (1967) and Gibbs and Gajdusek (1969) that two subacute progressive "degenerative" diseases of the human nervous system, namely Kuru and Creutzfeldt-Jakob disease, could be transmitted to chimpanzees. After an incubation time of from one to two years in the animals a slowly progressive encephalopathy developed that mimicked the corresponding human disease. The pathologic changes of these diseases are remarkable in that there are no inflammatory reactions. Intense gliosis and vacuolar degeneration of nerve cells are characteristic findings. A similar subacute spongiform encephalopathy, namely scrapie, is known to occur in sheep. The agents inducing these encephalopathic conditions have not yet been identified. The unusual characteristics of the scrapie agent suggest a structure akin to plasma membranes. Electron microscopy supports this theory by revealing abnormal collections of membranes in vacuolated neuronal processes. There is reason to believe that other degenerative diseases of the nervous system may also be caused by slow virus infections.

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### Prevention of Viral Hepatitis

In 1970, the national cooperative study of post-transfusion hepatitis reported that 30 ml of gamma globulin following transfusion failed to prevent or modify either short (IH) or long incubation (SH) disease. However, globulin does pre-



vent or modify IH following oral exposure and, in one study, serum containing a mixture of globulin and the IH agent produced no disease when given parenterally. The neutralization of the virus before injection may have been critical to this result. For IH post-exposure prophylaxis, an adult should receive 2 ml and a child 1 ml. Current evidence suggests that globulin provides poor, if any, protection against parenteral exposure to the SH (Australia antigen-positive) agent. Antibody to the Australia antigen has not been detected in the commercial globulin.

Screening blood donors by Au antigen testing will probably reduce transfusion hepatitis about 30 percent. Rigid donor selection would be more effective than Au antigen testing.

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### Platelet Typing

Platelet typing has developed rapidly during the past two years with the introduction and international standardization of microcomplement fixation methods. Almost all the histocompatibility antigens known on lymphocytes have been identified on platelets. Of the four additional platelet specific antigen systems identified only the  $PI^A$  and  $PI^E$  have been implicated in transfusion and neonatal thrombocytopenias. The sera from a large proportion of persons receiving more than ten transfusions, and of sera of women in late pregnancy have antibodies, often multispecific, against histocompatibility antigens on platelets and lymphocytes. Antibodies for platelet antigen systems other than  $HL-A$  are less common. Production of thrombocytopenia and rapid destruction of transfused platelets by these isoantibodies have been clearly demonstrated; while transfused "matched" platelets have a considerably longer survival in the recipient. Present practical considerations limit the clinical application of platelet typing. Entirely compatible donors, except for

family members, are relatively rare; however, complete compatibility may not be necessary. The present ability to store viable platelets for a few days makes routine use of "matched" platelets more feasible than heretofore. Current development of more sensitive and practical methods will considerably expand the diagnostic and therapeutic capabilities in thrombocytopenic disorders of immune origin.

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### Prenatal Diagnosis of Genetic Disease

Cells obtained from amniotic fluid and cultured by tissue-culture methods can be used for diagnosing some genetic diseases in utero. The sex of the fetus and the chromosome constitution can be readily ascertained by this method. It is also possible to diagnose certain inborn errors of metabolism by testing the cultured cells for enzyme deficiencies or accumulated abnormal substances.

Amniotic fluid can be obtained by transabdominal amniocentesis; it is generally recommended that 14 to 16 weeks gestation is the optimum time.

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### Herpes Virus

Renewed interest in herpes viruses as human pathogens stems from their possible roles in cancer and in infectious mononucleosis.

Herpes simplex virus occurs in at least two serological types, I and II. The former produces the common "cold sore." The latter produces cervical, vulvar and sometimes penile acute lesions.

Various investigators have shown that 70 to 100 percent of women with invasive cervical cancer have antibodies to the herpes II virus, whereas only 30 to 95 percent of patients with atypia or in situ carcinoma have such antibodies. In general controls show a distinctly lower percentage.

It is possible that the correlation of herpes virus and cervical cancer is simply another example of the higher incidence of venereal disease in women who have cervical cancer. In a study based in New Zealand there was little difference between three groups including controls, in situ, and invasive cancer.

The EB (Epstein-Burkitt) virus is a herpes virus first observed in cells cultured from Burkitt's tumors. Patients with Burkitt's lymphoma tend to have much higher viral antibody titers than do controls. A rise in titer occurs in previously negative patients in whom infectious mononucleosis develops. High titers also occur with naso-pharyngeal carcinoma. Thus far there appears to be a strong case for the EB virus as the etiologic agent in infectious mononucleosis. The case for oncogenicity is almost as strong although it is difficult to exclude the possibility that the virus simply infects and grows preferentially in some malignant or transformed lymphoid cells.

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### Diagnosis of Death Due to Insulin Overdosage

The proof that insulin overdosage has caused death is difficult. The half-life of insulin (12 minutes) precludes the estimate of elevated levels of insulin in circulation and tissues except in rare situations when an overwhelming amount of insulin has been injected into the patient's blood stream shortly before death. In such a situation, it is important that specimens from highly vascular organs be stored in the frozen state. The insulin can be extracted from these specimens with

acid alcohol. Also, it is important that control tissues be obtained and treated in the same fashion for comparison. It is important to survey the body for injection sites. The tissue around the injection site should be excised and comparable tissue from the contralateral side of the body should be taken for comparison. Again, the insulin may be extracted and the amount estimated by radio-immunoassay and bioassay. The first proof of murder by insulin was obtained in this fashion in England in 1957. Important history and ancillary laboratory information which is essential in putting together such a diagnosis, includes the blood glucose levels, cerebral spinal glucose levels, and glucose levels from any other biological fluid. It is important to note whether the patient had been exposed to a long period of fasting and alcoholism before his death, since profound hypoglycemic episodes can ensue. Also important is a very thorough examination of the pancreas to rule out any pancreatic tumors which could be the cause of hypoglycemic episodes, convulsion and death. Particularly difficult is the estimation of insulin overdosage in individuals who have been treated with insulin. In such situations, circulating levels of antibodies have developed which combine with insulin and result in variable estimates of circulating insulin level. Overdosage in this case can best be estimated by excision of the injection site. Levels of insulin at an injection site which are significantly greater than the total daily dose taken should be highly suggestive of an overdose.

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### Complications of Drug Abuse

Drug abuse is best defined as the use of drugs in such a way as to cause harm. Diseases associated with drug abuse are becoming common in most communities and must be considered in the differential diagnosis of almost any sick person.



The most frequent drug-induced diseases are those associated with legal, socially-acceptable drug abuse—alcohol, tobacco and sleeping pills. Alcohol-related diseases include hepatic cirrhosis, accidents, pancreatitis, peripheral neuropathy, Wernicke's encephalopathy, hypertension, hemolysis and gastroduodenal ulcer disease. Diseases associated with tobacco addiction include cancer of the lip, oral cavity, larynx, bronchus and urinary bladder, arteriosclerosis, coronary heart disease, pulmonary emphysema, fetal maladies and bed fires.

Physical dependence (addiction) and its related withdrawal syndromes are frequent with narcotics, barbiturates, alcohol, tobacco and some tranquilizers. The depressant drugs (alcohol, narcotics, tranquilizers and hypnotics) commonly kill by accidental or intentional overdose—alone or in combinations.

The intravascular injection ("mainlining" or "shooting up") of any drug of abuse results often in complications of serum hepatitis, thrombophlebitis, pulmonary embolism, cellulitis, abscesses, sepsis, bacterial endocarditis and gangrene of extremities (if arterial injection). Inhalation of vapors (glue, gasoline, aerosols, etc.) can cause bone marrow and liver damage, and sudden death from cardiac arrhythmias or suffocation.

The hallucinogens cause irrational behavior with "bad trips" and "flashbacks," and temporary or permanent psychosis, but chromosomal damage is yet unproven. Amphetamines rarely kill acutely but do induce hypertension, hyperpyrexia, a hypermetabolic state, temporary or permanent psychosis, ruptured berry aneurysms and hemolysis, and may be the common denominator in a new disease termed "necrotizing angitis of drug abusers." Marijuana is noteworthy for the absence of recognized harmful physical effects, unless administered intravascularly.

There is little doubt that the epidemic of recognized diseases (old, new and yet undescribed) associated with drug abuse will continue to increase for many years.

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#### igM\* Screening of the Newborn

The diagnosis of chronic intrauterine infection of the newborn has long been a problem because it is frequently clinically asymptomatic. Demonstration that the human fetus has immunologic competence has led to the monitoring of total cord blood igM levels by immunodiffusion. These studies indicate stable levels of igM from the 30th week of gestation to birth; thus levels in premature and full-term infants should be the same. Increased igM levels indicate increased fetal antigenic stimulation, such as from intrauterine infection. The mean cord blood igM level is about 11 mg per 100 ml, and 18 to 20 mg (about 1.5 standard deviation) is considered the most suitable point to indicate abnormality. Each laboratory must standardize its own mean and abnormality point. These levels give very few false negatives and a manageable number of false positives.

Increased cord igM levels are very successful in detecting intrauterine rubella, *Treponema pallidum*, toxoplasma, cytomegalovirus and enterovirus infections, in the order of decreasing sensitivity. They are much less successful in detecting acute intrauterine infections, including most bacterial infections. It should be noted that some very severe chronic intrauterine infections of the above types may cause hypogammaglobulinemia with very low igM levels for even newborns.

It may be anticipated that 2 to 4 percent of all newborns will have elevated cord igM levels by the above criteria and about one-third of these will prove to have had chronic intrauterine infections. These are mostly clinically silent, yet damaging to the infant in the long run.

Asymptomatic infants with elevated igM levels should be studied diagnostically with appropriate

\*Immunoglobulin M.

specific fluorescent igm antibody techniques for syphilis, rubella, toxoplasma, cytomegalovirus, etc. If these are negative the infant should be further studied for occult urinary infections, aseptic meningitis, viral conjunctivitis and diarrheal states, etc. The cause of the elevated cord igm levels that cannot be attributed to such diseases is not apparent at this time. Many workers advise

concurrently determining cord iga levels as an indication of maternal blood contamination, since cord blood has essentially a zero level.

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## Calcium Metabolism

IN THIS ISSUE THERE appears a review entitled "Recent Advances in Calcium Metabolism," by Dr. Gilbert S. Gordan, Professor of Medicine at the University of California, San Francisco. In his comprehensive article Dr. Gordan writes in a way to help medical practitioners to wend their way through an immense production of papers by clinical investigators which have evolved mainly from developments of methods for immuno-assay of parathyroid hormone and an intense laboratory investigation into a substance known as calcitonin.

The author wisely emphasizes the need for visualizing the newer information derived from sophisticated modern techniques in the context of the older work based largely on anatomic and clinical observations. He tries to bring the two together into concepts which will help the clinician to approach patients with skeletal problems more wisely and on a more rational basis. This highly worthwhile endeavor proves to be exceedingly difficult, primarily because fundamental factual knowledge at the basic physical and chemical level as to just how calcium behaves in both intracellular and extracellular environment is not available. Nevertheless, the practitioner who cares for the patient and the clinical investigator, too, would do well to study Dr. Gordan's carefully developed concepts, and be guided by his conservative therapeutic approach, which is based on a wide experience. Especially valuable is his attitude in dealing with the osteopenic (porotic) disorders, a broad point of view which this writer has not seen previously stressed.

Persons working on individual aspects of problems relating to calcium metabolism might take issue with quite a number of Dr. Gordan's expressed views. But, in the main, these differences

would be conceptual, the coming to an alternate conclusion, having used the same evidence on matters of which the basic facts are as yet obscure.

The most interesting and significant advances in the calcium field during the past decade seem to me to be in the altered conceptual attitudes of the investigators themselves. Although the bones are inevitably the ultimate area where calcium salts are stored and from which serum calcium concentration is replenished by homeostatic mechanisms in times of stress, the salts of the skeleton are no longer viewed as being in some sort of nebulous equilibrium with an extracellular calcium salt which is undersaturated in itself but supersaturated with respect to crystalline hydroxyapatite. Rather the salts of bone are conceived as being laid down and released behind closed doors, within a membrane which has the capacity to maintain a differential gradient.<sup>1</sup> This concept necessarily implies cellular (enzymatic) activity in both ingress and egress of calcium, in its deposition and release.

Furthermore, sophisticated methodology has disclosed that much of the calcium phosphate salts in the skeleton, which we were wont to consider crystalline, are in reality *colloidal* (non-crystalline, amorphous, nebulous aggregates), as originally proposed by Robinson<sup>2</sup> and Molnar.<sup>3</sup> Theoretically, such colloidal aggregates of calcium and phosphorus would be far more chemically mobile than would be hydroxyapatite crystals, and as such would be easy to resolubilize or move onward to the crystal habit, as local chemical factors, such as change in pH, might demand. And all this would be carried out in a compartment closely guarded from the extracellular fluids, the movement of calcium being actively transported in and out of the compartment.

Such notions have been carried over even into the subcellular levels. *In vitro*, mitochondria have been shown to take up immense quantities (to one-third their weight) of calcium phosphate under certain conditions, and to do this even preferentially to oxidative phosphorylation, their usually conceived main objective.<sup>4</sup> And these masses

of calcium phosphate within the mitochondria are found by x-ray diffraction to be in colloidal, not crystalline, state.

But how are agglomerated masses of calcium and phosphate maintained in colloidal phase for prolonged periods, a situation which would seem to be of enormous benefit to the organism in handling transport in bulk and maintaining the exact homeostasis of calcium ion in extracellular compartment, so necessary to normal biological function?<sup>25</sup> It has been shown by several groups of workers<sup>6,7,8</sup> that physico-chemical laws require solutions of calcium and orthophosphate to pass through a colloidal phase before reaching the crystal habit. In strongly supersaturated solutions this colloidal state is very brief, and complete crystallinity is reached within a few minutes. But, if one adds certain normal constituents of blood and urine to the supersaturated calcium phosphate solutions, the colloidal phase is greatly prolonged and no crystals are produced over many hours. Such "inhibitors," which also prevent *in vitro* calcification of ricketic cartilage, are represented by citric acid and pyrophosphate; but there is in normal urine a massive inhibitory potential, of which citric acid and pyrophosphate hardly represent one-tenth—the missing inhibitor potential is still unknown. But it seems a good speculative guess that within the skeleton and within the mitochondria inhibitors of this type are present when supersaturation takes place, and that substances of this ilk maintain the colloidal calcium phosphate phase, preventing crystal formation.

A further facet in the emerging picture of calcium transport at the molecular level is the discovery of substances in cell membranes<sup>9</sup> and even mitochondrial membranes<sup>4</sup> which sequester (or hold or bind) large quantities of calcium in a more or less neutral state. These relatively large protein moieties may require vitamin D or one of its active forms<sup>10</sup>—such as 25-hydroxycholecalciferol—as either a permissive or regulating agent in its production. The thought is that such local accumulation of calcium would not necessarily be in association with phosphate, but under appropriate chemical stimulation would be released as ions to join with phosphate, and this combination would then be maintained in colloidal packets of calcium phosphate.

Another study of experimental evidence offers further food for thought relative to the chemical nature of calcium phosphate salts in normal and

vicarious calcification. In the course of an effort to elucidate the mechanism of the von Kossa reaction, long used to identify calcium phosphate salts in biological material, some interesting facts have come to light.<sup>11</sup> Pure calcium phosphate crystals do not induce the instantaneous black color characteristic of the von Kossa reaction; but, if formed in the presence of even very small amounts of citric acid, they will do so. Colloidal calcium phosphate, so maintained by the presence of citric acid, will likewise yield the von Kossa reaction. Hence we can no longer look upon calcium and phosphate salts in tissues as crystalline as we formerly did because they yielded the black color to silver nitrate and light; they may just as well be colloidal calcium phosphate, for citric acid is a ubiquitous substance. Nine other carboxylic acids, none known to be present in nearly the concentration of citric, likewise have this capacity to induce von Kossa positivity to calcium phosphate crystals; and all of these have at least two carboxylic acid moieties in their make-up, and at least one hydroxyl group. Thirty other carboxylic acids not fulfilling these criteria fail to induce von Kossa reaction; and pyrophosphate will not do it. These carboxylic acids, which induce the black stain, become integral portions of the apatite structure; they cannot be washed off and presumably, because of calcium-to-phosphate ratio differences, they are thought to replace phosphate in the crystal lattice. It has long been known that citric acid is a normal constituent of bone salt; may this not be its important function here?<sup>2</sup>—that is, to maintain calcium phosphate in colloidal state until such time as its activity in this regard is overcome by further chemical pressure, or it is freed by opposite forces to permit reionization?

These new facets of knowledge relative to the behavior of calcium in body fluids may pave the way for provision of better basic information and thus to better interpretation of clinical data, so badly needed.

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## Advances in the Study and Treatment of Acute Myocardial Infarction

THE CLINICAL IMPORTANCE of acute myocardial infarction in producing disability and death is emphasized dramatically by the estimates which suggest that in the United States alone, in 1971, more than 1,000,000 persons will have myocardial infarction and more than 250,000 of them will die of the attack. Moreover, one-third of these patients will be under the age of 65 years. These facts suggest the need for greater research on this important disease. While most research, at present, is directed toward better diagnostic and therapeutic approaches in patients with coronary artery disease, there is little indication that these studies will affect mortality significantly. Innovative studies into the causes of acute infarction and to the predisposing causes of atherosclerosis are needed.

In the Speciality Conference, "Research on the Diagnosis and Treatment of Myocardial Infarction," by Braunwald and associates published in this issue of *CALIFORNIA MEDICINE*, much attention is given to new clinical and laboratory features of acute myocardial infarction.<sup>1</sup> Emphasis is directed toward early diagnosis and the possibility of surgical intervention. Additional publications<sup>2,3</sup> have recently discussed the possibility of reducing the morbidity and mortality from acute myocardial infarction by surgical techniques. Hence this review of the newer diagnostic and prognostic advances seems timely.

In establishing the diagnosis of acute myocardial infarction, the electrocardiogram remains one of the primary methods available to physicians, although confirmation by measuring alterations in serum enzymes and for the detection of smaller areas of necrosis not usually producing diagnostic electrocardiographic changes are important. In the specialty conference, Dr. Karliner describes two new techniques for detecting myocardial necrosis. Detection of elevations of glyceraldehyde phosphate dehydrogenase (GAPDH) in patients with acute myocardial infarction appears to be highly reliable and technically simple. The great advantage over detection of elevations in SGOT and LDH is that GAPDH is elevated earlier and remains elevated for only a short time. This allows the detection of a recurrent infarction, or extension of the initial area of necrosis. Measurement of isozymes of LDH, which is also discussed, potentially has advantages but to date no convincing evidence is available that these enzyme fractionations will lead to improved diagnosis.

Various methods to determine what areas of the myocardium are inadequately perfused have been devised recently. Coronary arteriography is the most direct method, but because of the risk to patients with acute infarction, it is not frequently employed. The techniques utilizing injections of microaggregated radioactive labelled albumin into the coronary arteries for external scanning with a detector is of interest. The technique needs further quantitation, however, and does not remove the need for catheterization of coronary arteries. Its risks, when widely employed, are not known and it fails to delineate precisely the anatomical changes in the coronary arteries, so that surgical intervention can be considered.

Radarkymography allows the physician to detect areas of ventricular wall which contract in an abnormal manner (aneurysms) in acute and chronic myocardial infarction. This technique is another of the non-invasive methods available for studying ventricular performance, and its clinical value in patient study may well be great after appropriate validation.

In order to evaluate better the late clinical course of patients following acute myocardial infarction, quantitation of the size of the infarction is needed. Determination of ventricular size as described by Ross in this published specialty

clinic allows determinations of left ventricular size which is correlated with a higher incidence of late deaths. Only more clinical experience with this technique will clarify its place in the care of patients with acute myocardial infarction.

A new and interesting technique to determine the size of an infarcted area of myocardium has been developed by Dr. Maroko and colleagues. It is based on determining the area of injury by utilizing direct electrode recordings from the myocardium and quantitating the degree of ST segment elevation.<sup>1</sup> This technique has been studied in animals with experimental coronary artery occlusion and has been correlated with the decline of creatine phosphokinase in the ischemic tissue. Utilizing these techniques to quantify the degree of myocardial damage, the effects of glucagon, beta-blocking agents, digitalis glycosides and anti-arrhythmic agents on infarcted tissue have been studied.

While all of these techniques are of interest in the laboratory, they cannot be applied in man. In addition, a number of questions regarding the value of studying ST segment elevation for quantifying myocardial damage have been raised.<sup>4</sup> These include the detection of subendocardial and intramural myocardial infarction, the need to apply pressure to the myocardium by electrodes which alter ST elevations, and the difficulty in placing electrodes precisely for repeated study.

The early surgical intervention in patients with acute myocardial infarction who develop rupture of papillary muscles, rupture of the ventricular septum and large ventricular aneurysms has become commonplace.<sup>5,6</sup> The results of such operations have been good and they depend to a large extent on the severity of myocardial damage in each individual patient. The resection of infarcted tissue and the use of saphenous by-pass grafts from aorta to coronary artery are being carried out under experimental protocols in patients with acute myocardial infarction. These techniques need further evaluation before being adopted widely.

Although much of the investigation described by Braunwald and colleagues is promising, many more studies with these and other new methods are necessary before clinical care of patients with acute myocardial infarction can be expected to improve. In addition, the development of new methods for studying and treating patients after

symptomatic disease develops will likely have only a small effect on mortality from this disease process.

Among the several fields of investigation which have promise for reducing mortality are the identification and treatment of high-risk individuals, understanding of genetic abnormalities of lipid metabolism, public education regarding risk factors and the desirability of seeking early medical attention after infarction, and the development of effective circulatory assist devices. One other area of particular promise is the identification of precipitating factors in acute infarction.<sup>7</sup> While acute infarction and sudden death have both increased drastically, there is less substantial evidence that atherosclerosis has increased dramatically.<sup>7,8</sup> The factors which precipitate acute infarction may be identified by studying intently patients with impending infarction. These studies must include assessment of metabolic, hematologic, social and psychological, environmental and cardiac factors related to infarction. While no dramatic breakthroughs appear on the horizon, substantial long term progress appears possible.

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## Of Pharmacists, Physicians And Health Care

In his wide ranging discussion which appears elsewhere in this issue Dean Goyan forthrightly addresses himself to many problems in patient care which he recognizes as going far beyond



"the physician-pharmacist interface." Pharmacy is indeed in crisis, finding itself since World War II "increasingly estranged from the widely publicized but barely existent 'health care team'" at a time when problems relating to the use and misuse of both prescription and over-the-counter drugs are becoming of truly massive importance to all who are concerned with health care. Dean Goyan is an acknowledged leader who envisions the pharmacist in an important new role in which his particular knowledge of drugs and drug preparations will result in their more appropriate and more precise use in patient care and maintenance of health. The problems of pharmacy are acute indeed and many of them are shared to a greater or lesser degree by the many other professions which together compose the "health care team."

In his book *The Greening of America* (to which Goyan refers) Charles Reich identifies what he calls Consciousness I, II and III Americans. Whether this distinction proves to be valid and whether the thesis that Consciousness III Americans will eventually displace the Consciousness I and II types will prove correct, remains to be seen. Briefly the Consciousness I American is described as having the traditional outlook of the American trying to get ahead, competitively pitting his success against the success of others in essentially unregulated fashion—free enterprise, if you will. The Consciousness II American is described as accepting the values of organization and the necessity for control, even though this means domination of the individual and his submission to the corporate ideal, whether public or private or the State itself, a view which Reich associates with "liberalism." And the Consciousness III American is described as "the new generation" which seeks liberation from the imperatives of society, sees through "phoniness" with astonishing clarity, is deeply committed to personal fulfillment for all as well as to the betterment of communities and of society as a whole, and which seeks to share actively in the decision-making processes through what is coming to be called "participatory democracy."

It is becoming obvious, as Dean Goyan intimates, that what might be called the Consciousness III attitudes are gaining considerable acceptance and influence in various allied health professions, and in consequence the traditional organizational hierarchy in patient care, like corporate industry or the corporate state itself, is being increasingly challenged, particularly by the

younger members of these professions, and this includes medicine. The dictation or direction by physicians or organized medicine of what shall or shall not be the function of other professions is no longer well received, and even the doctor's "orders" in the hospitals and elsewhere are beginning to be questioned by nurses, pharmacists and others, and even by consumers where matters of cost are involved. All of this seems to be far more deeply rooted than it might first seem, and likely it foreshadows some very fundamental changes in the governance of patient care and the delivery of health care services, perhaps sooner than many might think possible.

So far the nature and group dynamics of "health care teams" have received very little consideration or study by the medical profession. Others have been giving it far more thought. Physicians are apt to take it for granted that if there are to be health teams they will always be the captains. In certain situations, as when a life is in the balance on the sickbed or in the operating room for example, this will be uncontested. Here there must be a team captain, he must be a physician, and like a general on a battlefield he must make the best decision he can with whatever information and resources are available, and his decision must be obeyed by those in attendance. But in less critical circumstances this traditional command authority may become more diffuse and other professionals are found more directly involved in the decision-making processes of patient care. The thought, perhaps specter is a better word, of patient care being directed by committees of health professionals, very possibly with consumers added as voting members, inevitably comes to mind. Yet this in fact already occurs (although so far without consumer or public participation) in certain areas of rehabilitation and in the actions of tumor boards for example, and the experience has been by no means all bad.

Dean Goyan has raised as many questions for physicians to ponder, as he has for pharmacists. It is time that medicine gives as much thought to the roles of the various allied health professions in the governance of patient care and health care as has already been given by a number of other professions which are properly concerned. "The times they are a-changin'." Patient care and the maintenance of health are now everybody's business and participatory democracy is surely in the air.

## A Matter of Reverences

THIS SEEMS to be a moment in history which is in many ways unlike anything that has gone before. We are quite evidently in a period of profound moral upheaval. The evidence is all around us. It need not be documented. It is reflected in citizen protests, in defiance of the law, in court decisions and in the deeply disturbed responses from the churches.

The culprit is modern science. It has given rise to an industrial technology which has made possible a better quality of life for a very much larger number of people, which is good. It has also produced pollution which in some situations has already become almost intolerable, and this is bad. It has produced nuclear power which can destroy both the industry and the greater number of lives it has made possible, but also can develop the energy to support both in unprecedented richness. And it has created modern medicine, which is giving modern man an increased capability to control himself, prolong his life, improve his health and well-being, and influence the future of his species. Modern science is changing the whole fabric of our culture and this is the root cause of the moral upheaval we see around us.

It is suggested that many of the fundamental ethical problems which face medicine and the society it serves can be reduced to very simple terms. The issues really revolve about (1) reverence for each and every human life, which is not debatable for a physician, and (2) reverence for humanity as a whole, which really is not debatable either. Fortunately most of the time these two are not in conflict. But sometimes they are, and this is where many of the unsolved ethical problems lie, for both society and for medicine.

The decision to legalize abortion was made by society as a whole which accepted this idea and then changed the laws. It was certainly not a decision of medicine. The decision with respect to approval of abortion is, therefore, a social one,

and beyond that it is one of individual conscience, whether of doctor or patient. This is the California Medical Association's position on the matter.

There are comparable situations, where reverence for each and every human life may come into conflict with reverence for humanity as a whole. For example, how long should the resources of humanity be used to sustain a human life when the prospects for recovery or a useful existence seem hopeless? And who is to make the judgment? For whom should scarce life-sustaining resources, long-term renal dialysis for example, be used when there are not enough of these resources for all who need them? And who is to render this judgment? And what about the many ethical problems of organ transplants, and who is to make these judgments? And what about using our scientific know-how to limit or eliminate some of the bad genes from the genetic pool of humanity, and how is this to be decided, and how is it to be done?

Such issues, which introduce conflict between reverence for humanity and reverence for each and every human life and the health and well-being of both, are not likely to be decided by dogma or social theory, or by pitting social theory against dogma. It is more likely that each of these problems will have to be considered individually, and that an acceptable ethic for medicine and society will eventually develop from what occurs as the result of such deliberations and the experience which accrues from them. Choices are already being made in Western society, choices as to who will be born and who will not, and choices as to who will receive some scarce and costly treatment in order that he, rather than someone else, shall live. The profession has begun to adjust to changes in the society it serves. Medicine has been notably reluctant to make these decisions by itself, and rightly so, but nevertheless cannot help influencing the decisions.

These are complex problems, but they cannot be ignored. They won't go away. They go far beyond the abortion issue which so far has received most of the attention. The House of Delegates of the California Medical Association was well advised when it voted at the recent meeting to establish "a continuing advisory committee to consider the response of the medical profession to the evolving scientific, technological and philosophical trends in our society as they affect human life."



# NEW CMA OFFICERS AND REPRESENTATIVES

Dr. Roberta F. Fenlon, San Francisco, has taken the reins of leadership for the California Medical Association, becoming the first woman president of the organization. She was installed in that office at the Annual Session, March 13-17 in Anaheim, and Dr. Jean F. Crum, Downey, was voted president-elect.

Two Los Angeles physicians, Dr. William F. Quinn and Dr. Joseph F. Boyle, were reelected House of Delegates speaker and vice speaker, respectively.

In a special organizational meeting of the Council held following the Annual Session, Dr. John T. Saidy of San Mateo was elected chairman, succeeding Dr. Harold Kay of Oakland who was elected a delegate to the American Medical Association. Dr. Saidy, who had been vice chairman of the Council, is replaced in that position by Dr. E. Kash Rose, Napa. Dr. Philip F. Voigt of Long Beach was elected by the House to fill a three-year term as councilor from District 4, Office 1.

The following is a complete list of newly elected officers, AMA representatives, and Blue Shield trustees:

## California Medical Association

President: Roberta F. Fenlon, M.D., San Francisco  
President-Elect: Jean F. Crum, M.D., Downey  
Speaker, House of Delegates: William F. Quinn, M.D., Los Angeles  
Vice Speaker, House of Delegates: Joseph F. Boyle, M.D., Los Angeles  
Council Chairman: John T. Saidy, M.D., San Mateo  
Council Vice Chairman: E. Kash Rose, M.D., Napa  
Scientific Board Representative: C. John Tupper, M.D., Davis (reelected)  
New Councilor (three-year term): Philip F. Voigt, M.D., Long Beach—District 4  
Councilors (reelected for three years):  
Nicholas P. Krikes, M.D., San Bernardino—District 2  
Jokichi Takamine, M.D., Los Angeles—District 4, Office No. 2  
Samuel Horowitz, M.D., Los Angeles—District 4, Office No. 4  
George C. Andersen, M.D., Hermosa Beach—District 4, Office No. 7  
John T. Saidy, M.D., San Mateo—District 7, Office No. 2  
Thomas N. Elmendorf, M.D., Willows—District 11

## The AMA delegation

### New Delegates

Dr. Joseph F. Boyle, Los Angeles (new office effective January 1, 1971)  
Dr. Harold Kay, Oakland (fills new term January 1, 1972)  
Dr. James C. MacLaggan, San Diego (fills current unexpired term of Dr. Francis E. West and new term)

### New Alternates

Dr. H. Dean Hoskins, Oakland (fills new term January 1, 1972)  
Dr. Raymond N. F. Killeen, Los Angeles (fills current unexpired term of Dr. Joseph F. Boyle and new term)  
Dr. Ralph M. Milliken, Los Angeles (fills current unexpired term of Dr. Robert L. Watson, Jr., and new term)

Dr. Jokichi Takamine, Los Angeles (new office effective January 1, 1971)  
Dr. Elmer C. Werner, El Centro (fills current unexpired term of Dr. James C. MacLaggan)

### Reelected Delegates

Warren L. Bostick, M.D., Irvine  
Vincent P. Carroll, M.D., Laguna Beach  
Dudley M. Cobb, Jr., M.D., Los Angeles  
Eugene F. Hoffman, M.D., Los Angeles  
Albert G. Miller, M.D., San Mateo  
Emmet L. Rixford, M.D., San Francisco  
Wilbur G. Rogers, M.D., Glendale  
John M. Rumsey, M.D., San Diego  
Samuel R. Sherman, M.D., San Francisco  
Ralph C. Teall, M.D., Sacramento

### Reelected Alternates

Walter H. Brignoli, M.D., St. Helena  
Thomas N. Elmendorf, M.D., Willows  
George K. Herzog, Jr., M.D., San Francisco  
Herbert A. Holden, M.D., San Leandro  
Arthur F. Howard, M.D., Fresno  
Ben D. A. Miano, M.D., San Bernardino  
Laurance A. Mosier, M.D., Garden Grove  
Gregory C. Murray, M.D., Los Angeles  
John V. Pollack, M.D., Los Angeles  
Ralph W. Schaffarzick, M.D., San Francisco

## California Blue Shield Board of Trustees (three-year-term)

### New Members

Ross L. Ballard, M.D., San Bernardino  
Bradford P. Cohn, M.D., San Francisco  
Robert E. Dreibelbis, M.D., Tustin  
Mr. Don Muchmore, Long Beach  
Henry S. Williams, M.D., Los Angeles

## Medical Executive's Conference

Chairman: Edgar H. Colvin, Monterey County Medical Society  
Vice Chairman: Robert J. Marvin, Santa Barbara County Medical Society

# CASE REPORTS

## Anaphylactic Reaction to Oral Penicillin

JOHN P. GEYMAN, M.D., *Santa Rosa*

IT HAS BEEN WELL KNOWN for many years that penicillin is the most common cause of allergic drug reactions. The possibility of anaphylactic reactions to parenterally administered penicillin is fully appreciated by all clinicians. Less well known, however, is that oral penicillin can cause anaphylactic reactions and even death.

The purpose of this report is to present a case of anaphylaxis to oral penicillin, which is believed to be the first such case reported in California. The potential immediacy in onset of allergic symptoms after the ingestion of oral penicillin will be stressed. The literature concerning anaphylactic reactions to oral penicillin will be reviewed.

### Report of a Case

The patient, a 38-year-old Caucasian woman, was seen in the office with a one-week history of increasing cough and intermittent low-grade fever. In the last several days, the cough was productive of slightly colored sputum, but hemoptysis was denied. For the last two days the patient had had pleuritic pain in the area of the right lower rib cage.

Past history was featured by a confirmed diag-

nosis of sarcoidosis made 14 years previously. The patient had required antibiotic treatment for recurrent bronchitis on many occasions in the past, often including penicillin. She had never had an allergic reaction to penicillin or to any other drug; nor was there a family history of allergic sensitivity to drugs. She said she had never had asthma, hay fever or other allergic problems.

On physical examination, positive findings were confined to the chest. Rhonchi were present bilaterally in the lung bases; rales or dullness were absent.

A diagnosis of acute bronchitis was made, and the patient was given prescriptions for oral penicillin and an expectorant.

On the following day, the patient took her first dose of penicillin at 7:55 a.m., a tablet of 400,000 units of penicillin G. Within two or three minutes, redness and pruritus of the hands developed. She telephoned at that time, and her husband was asked to take her immediately to the office. During the next five minutes as she was driven to the office, both hands became swollen and angioedema developed around the eyes and the lips. When seen in the office at 8:00 a.m., she was becoming nauseated, feeling faint, and dyspneic. She was starting to complain of discomfort in the chest. She was somewhat cyanotic, had a weak, thready pulse and blood pressure of 50/0 mm of mercury. There were a few bilateral wheezes present, and pulmonary exchange was poor.

The patient was immediately given 0.5 ml of 1:1000 aqueous epinephrine deep subcutaneously. An airway was established and the patient was ventilated with a pulmonator bag and oxygen. Benadryl® 50 mg was given intramuscularly. After about two minutes the patient's condition was not improved, and 0.25 ml of 1:1000 aqueous epinephrine was given intravenously, and intravenous infusion of normal saline solution was begun. Solu-Medrol® 40 mg was also given intravenously. The patient then began to feel better, her blood pressure rose to 95/60 mm, her pulse became stronger, and cyanosis disappeared as

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Reprint requests to: Community Hospital of Sonoma County, 3325 Chanate Road, Santa Rosa, Ca. 95402 (Dr. J. P. Geyman).



pulmonary exchange improved. She was observed another 20 minutes as her condition stabilized and then was transferred to the hospital.

The patient was in hospital for 24 hours, and became asymptomatic and fully ambulatory during that period. Wheezes disappeared shortly after admission, and her sensorium became normal. No skin rash or other symptoms appeared, and angioedema resolved in about 24 hours. Treatment included methylprednisolone (Solu-Medrol®) intravenously and diphenhydramine hydrochloride (Benadryl®) 50 mg four times a day.

Laboratory data obtained during the stay in hospital included: Hemoglobin 16.2 per ml gm; hematocrit, 50 percent; leukocytes 14,100 per cu mm with 84 percent neutrophils, 7 percent banded forms, 6 percent lymphocytes and 3 percent monocytes (no eosinophilia); and urinalysis within normal limits. An x-ray film of the chest was reported as showing bilateral apical disease radiographically unchanged since previous films dating back to 1952, when sarcoidosis was diagnosed.

The patient was discharged after one day in the hospital with prescriptions for Benadryl 50 mg four times a day and tetracycline 500 mg four times a day orally. She recovered uneventfully from both the allergic reaction and bronchitis. She was asked to obtain a bracelet showing allergic sensitivity to penicillin.

## Discussion

This case prompted a review of the literature on the subject of anaphylactic reactions to oral penicillin, and some interesting facets of this problem were uncovered.

In three large series, totalling over 45,000, of patients who were given penicillin by mouth for periods of five to thirty days, there were no anaphylactic reactions noted.<sup>1-3</sup> Welch et al surveyed over 800 hospitals and 1600 physicians for severe reactions to antibiotics from late 1953 to early 1957. They found 611 anaphylactic reactions to penicillin given intramuscularly, with 63 deaths, and 49 anaphylactic reactions to oral penicillin, with no deaths.<sup>4</sup> In 1960, Batson reviewed the English literature and found a total of 26 cases (with two deaths) and reported two more non-fatal cases.<sup>5</sup> Since 1960, several other cases of anaphylactic reactions to oral penicillin have been reported, but the total number reported in

the world literature is still probably less than a hundred cases.<sup>6-11</sup>

It is commonly accepted that a past history of allergic problems increases the risk of a patient having an allergic reaction to penicillin. It also has been frequently observed that patients having such a reaction often have a family history for allergic reactions to penicillin. But what is most disturbing is the observation that a majority of patients having anaphylactic reactions to oral penicillin have given a history of other manifestations of penicillin allergy in the past.<sup>5,6,8</sup> This reflects the ease with which we can disregard apparently minor symptoms a patient may have had after a previous exposure to penicillin.

Anaphylactic reactions have been recorded to all forms of exposure to penicillin. In Batson's study of 28 cases of such reactions, anaphylaxis was recorded after use of tablets, lozenges, liquid form, and powdered form taken in water. Batson also reported anaphylactic reactions after direct skin contact, accidental inhalation and skin testing.<sup>5</sup> In a review of the literature in 1957, Lewis found cases of anaphylaxis after instillation of penicillin into wounds and sinuses, use of penicillin aerosol and eye ointment.<sup>13</sup>

Initial manifestations of anaphylactic reactions to oral penicillin often occur surprisingly rapidly. In Batson's study, 25 of 28 patients had onset of symptoms in less than 15 minutes.<sup>5</sup> Many cases in the literature have featured onset of symptoms in less than one or two minutes. In these instances, it is likely that penicillin absorption has taken place sublingually or through buccal mucous membranes.<sup>14</sup> Since anaphylactic reactions to oral penicillin generally occur shortly after ingestion of the medication, observation of the patient in the physician's office for 20 to 30 minutes after the first tablet may be useful.

Anaphylactic reactions to oral penicillin may be manifested by a variety of symptoms not different in kind from those of anaphylaxis following parenteral penicillin. In Batson's study of 28 patients, the single commonest symptom was unconsciousness. Other signs and symptoms often noted in anaphylactic reactions to oral penicillin include hypotension, nausea, vomiting, abdominal pain, facial numbness or pruritus, respiratory distress, cyanosis, chest pain and convulsions.<sup>5</sup>

At present there is no simple laboratory procedure available to clinicians in everyday practice permitting detection of potential anaphylactic re-

actors to penicillin. There are, however, two types of skin tests which hold promise for this purpose, though they are still under study and not yet available for general use.<sup>15,16</sup> Immediate skin tests with BPL (benzylpenicilloylpolylysine) and MDM (minor determinant mixture) appear to be safe and reliable in detecting skin sensitizing antibodies (reagents) associated with high risk of immediate allergic reactions to penicillin, including anaphylaxis.<sup>15</sup> They may be useful in selected cases, but should be performed by specialists familiar with these techniques and associated with competent laboratory facilities. Hemagglutination assays of serum are of no value in predicting immediate reactions to penicillin.<sup>15</sup> The indirect basophil degranulation test can detect circulating antibody, but is still in an experimental stage and not yet technically satisfactory.<sup>16,17</sup>

The most valuable single drug used in treatment of anaphylaxis is epinephrine, which is ordinarily injected deep subcutaneously in a dose of 0.5 ml of the 1:1000 dilution. Massage of the injection site will facilitate its absorption. In the event of vascular collapse and poor absorption, 0.25 ml of 1:1000 epinephrine, diluted in 10 ml of saline solution can be given slowly intravenously.<sup>18</sup> If it is difficult to find a vein immediately, the base of the tongue is a site which allows rapid absorption.

Establishing an adequate airway is also of primary importance. Oxygen by mask is helpful as long as the airway is established. In the event of complete airway obstruction caused by laryngeal edema, endotracheal intubation or tracheostomy must be performed. If one does not have suitable equipment at hand, a needle (14 gauge or larger) may be inserted through the cricothyroid membrane to gain a temporary airway. Other measures which may also be necessary include the administration of an antihistamine and hydrocortisone sodium succinate (Solu-Cortef®) 200-300 mg intravenously. A primarily alpha-adrenergic agent such as norepinephrine (Levophed®) may be necessary in the presence of persistent vascular collapse.

## Summary

A case of anaphylactic reaction occurring several minutes after administration of penicillin by

mouth has been described. The literature has been reviewed for anaphylaxis to oral penicillin, and while it is a rare occurrence, it may well be more common than reported cases indicate. Symptoms of anaphylaxis to oral penicillin can be surprisingly rapid in onset and diverse in nature. Patients giving history of "passing out," facial numbness, convulsions, or vomiting after previous exposure to penicillin may have had anaphylactic reactions. Penicillin in any form should be avoided in any patient giving a suspicious history of allergic reaction to any type of penicillin, however "mild."

## TRADE AND GENERIC NAMES OF DRUGS

*Solu-Medrol*® .....methylprednisolone  
*Benadryl*® .....diphenhydramine hydrochloride  
*Solu-Cortef*® .....hydrocortisone sodium succinate  
*Levophed*® .....norepinephrine

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# Synanon: A Therapeutic Life Style

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THE CURRENT INTENSE search for an effective addiction treatment program follows in the wake of nation wide drug abuse of epidemic proportions. Besides the generally recognized ineffective prison approach, two approaches are most prominent and have a great measure of acceptance: (1) the use of chemical "blockades" such as methadone and cyclazocine, and (2) "therapeutic communities."

Synanon is the foremost "therapeutic community" in the country for drug rehabilitation. It was founded in California in 1958 by Charles E. Dederich. The organization has pioneered an alternative life style that has involved thousands of people, most of whom have stopped their former drug use patterns. The Synanon model has been copied in many parts of the country, especially New York.

Since its inception, Synanon has been a controversial organization whose audacious style has attracted many friends and supporters; at the same time it has produced its share of detractors. Very few people interested in the problem of drug abuse feel neutral about Synanon. Apart from Synanon's enormous direct impact on helping to solve the drug problem, the element of controversy about the organization and its life style has evoked a considerable amount of highly significant and valuable dialogue.

The dictionary definition of Synanon, "a pri-

vate organization assisting those who wish to be cured of drug addiction,"<sup>1</sup> refers to only one dimension of the overall Synanon system. The organization has steadily moved beyond the work of treating drug addiction and crime. Charles Dederich, the founder and chairman of the Board of Regents at Synanon, has repeatedly stated that Synanon is not primarily interested in curing drug addiction, but that this seems to occur as a side effect of an individual's participation in its life style. According to one of the authors in a previous publication:

Synanon's overall program encompasses a new kind of group therapy; an approach to racial integration; a humane solution to some facets of bureaucratic organization; a different way of being religious; a humanistic method of encounter therapy; an unusual kind of communication; and an exciting, fresh approach to the cultural arts and philosophy. One side effect of intense participation in these diverse human experiences is that those participants who were criminal addicts have found a new existence and now lead constructive lives.<sup>2</sup>

A part of Synanon's character that has become more articulate is its significance as an alternative life style. The function of Synanon is this way, as a vehicle for constructive personal and social change, has become clearer as the theory and method is increasingly utilized by people who were never addicts or criminals and who have no history of serious character disorders. Despite the importance of Synanon as a new life style for

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<sup>1</sup>Random House Dictionary of The English Language. New York, Random House, Inc, 1967

<sup>2</sup>Yablonsky, Lewis: Synanon: The Tunnel Back. New York, Penguin, 1967, p viii

many people, Synanon's breakthrough in this other aspect of the human condition is not the focus of this paper. The emphasis here will be essentially on Synanon's effect on character-disordered drug abusers, most of whom have had previous professional help that has failed.

## The New Situation

A drug user with a past of institutionalized treatment of another kind, generally finds himself in a new situation in Synanon. In most standard treatment programs, a patient or inmate subculture usually develops within the overall approach. This tends to produce a "we-they" conflict and split between the professional personnel and the "clients." The "client society" tends to be underground and to develop norms, patterns of behavior and goals different from and more often than not in conflict with the "treatment establishment." This is partly due to the fact that most "clients" have had severe difficulties with authority a good part of their lives. Synanon does not have a "we-they" caste system where the client is relegated to a lower position in the organization. Rather it provides an open ended stratification situation. A full possibility for upward mobility is available in the organization. There is not only upward social mobility in Synanon, but healthy status-seeking is encouraged.

Synanon assumes, with some supportive evidence, that a person's position in its hierarchy is a correlate of social maturity and "mental health." An old Synanon adage is "character is the only rank." Since the development of "character" is related to success in the organization, certain behavior is encouraged, such as speaking out in a Synanon game<sup>3</sup> when someone feels or observes a "wrong." This is encouraged regardless of the wrongdoer's status in the organization. In fact, to be silent in the face of "injustice" carries with it the moral condemnation of the group. Unlike the code of the streets, "copping out" on each other for behavior that is either self-destructive or harmful to the individual or the group is both condoned and actively fostered. This does not occur in the usual institutional "we-they" atmosphere.

Another significant and unique aspect of Synanon is that individuals with a criminal-addiction past are living and integrated with people from

all walks of life. In recent years, Synanon has involved thousands of people from all segments of the society. The Synanon population consists of almost every ethnic, religious, socio-economic and age group, and many of the participants were not themselves addicted to drugs. These people have moved into Synanon, often with their families, to take part in its new life style. This has virtually eliminated the larger society's dichotomy of "square" and addict. The non-addicts who have moved into Synanon generally view the larger society and its many problems of war, ecological pollution and ahumanism with disdain. They have moved in to pursue a life style in Synanon that they firmly believe is more hopeful.

Al Bauman, never an addict and never troubled with a "character disorder," currently director of education for Synanon, stated it this way: "I used to spend at least fifty percent of my time and energy in my life 'out there' defending. I used to be against things, including myself. Here at Synanon I finally found a place where I can be affirmative and say *Yes*."

## The Synanon Game

Synanon, essentially through the genius of its founder, Dederich, has invented and pioneered many group innovations. These include the weekend "marathon trip," educational searches and "the game."

The most important widely and continually used group process in Synanon is *the game*. All members participate in its process at least several times a week. In part, it is an intimate group interaction situation in which a member can openly express his problems, fears and hostilities to his fellows. He can expect a response that enables him to see his personal truths in a new and exciting perspective. The game also enables members to tell their fellows what they *really* think of them without retribution. Members can often solve the confusions and conflicts of their occupation and interpersonal relationships. A participant in a game can be as spontaneous, creative, rigid, angry, loud, or passive as he chooses with no authority rules save one, the proscription of physical violence.

The game often helps to regulate behavior in Synanon. Transgressions are often prevented by the knowledge that the next time the game is played a member's deviance will rapidly and

<sup>3</sup>The Synanon Game is Synanon's unique form of therapeutic group interaction. It will be discussed further in this paper.



necessarily be brought to the attention of the Synanon community. The participant is living in a community where others know about and (perhaps more importantly) care about his behavior. As was previously indicated, in contrast to the code of the streets, "copping-out" on each other for behavior that is either self-destructive or harmful to the group is both condoned and actively fostered.

Another major impact of the Synanon game is its ability to convey to each member a sense of responsibility and its corollary, a sense of personal value and significance. To people who have suffered from chronic feelings of weakness or helplessness, who characteristically see themselves as victims, the game becomes very meaningful when they are shown that their behavior can have a direct effect on other people and that it is within their power to change the overall society in a positive way.

### Synanon's Contribution

In general, at this time Synanon does not see "rehabilitation" as necessarily returning the addict to the outside world. Synanon's concept of itself as a social movement suggests an awareness of all the multiple problems facing mankind from pollution of the environment to racism to violence. Synanon has helped solve some of these problems. For example, the organization donates some of its surplus goods to poverty areas such as Watts. They have also made their group methods available for wider use. For example, they have established a contract with the Oakland Police Department under which all rookie policemen play the Synanon game in the hope of improving police-community relations.

Synanon sees its role in the revolutionary terms of creating a model society and demonstrating it to the world. It is Synanon's assumption that if this is done effectively, more and more people will join the movement.

Since Synanon's inception, professionals from many disciplines have involved themselves and made contributions to its growth and development. The ideal relationship, according to Synanon, is for the professional "to relate first as a human being and secondly as a professional." Synanon believes that in this way the professional can make the most meaningful contribution.

Over the past decade hundreds of physicians

and dentists have provided free medical and dental care to Synanon's residents. Now there is a fully equipped medical department with a full range of services including laboratory testing and 24-hour coverage, all volunteer. The head of the Synanon medical department is Carl Deissler, M.D., a member of the Synanon Board of Regents.

An example of Synanon's unique social accomplishments, and a source of great pride, is its school. Synanon organized its own educational situation for its increasing resident population. At present there are 150 children in the Santa Monica Synanon school. The children range in age from six months to sixteen years.

More recently, teenage dropouts and drug abusers from the hippie world have been added to the Synanon population, along with children without former problems whose parents believe in the educational program of the Synanon school. The educational complex directed by Al Bauman is expected to extend eventually from nursery school to college.

The children live in the school among their peers, "kibbutz fashion," with a male and female family head responsible for about a dozen children. The experience so far indicates that a child's separation from its parents has been much more difficult for the parents than the children. The children seem to thrive emotionally with their peers and learn in an atmosphere that attempts to encourage the child's natural curiosity. (Children and parents visit with each other periodically but the classical concept of the nuclear family is not in effect in Synanon.)

Some of the universal values and meanings of Synanon are dramatized by the general shared attitude felt by the adults of Synanon for their children in their school. This is illustrated by the following vignette: On the day that one of the authors visited the Synanon school, a Synanon family of some years' standing had left, taking their three children with them. Dede Harvey, the schoolmaster, was shocked and dismayed. "This proves that the insanity of dope fiends lies just beneath the surface, no matter how long they have been here. One of their kids is mentally retarded and has severe cerebral palsy. When she came to us she couldn't speak, dress herself, or eat properly. In just a few months of being in this environment, and getting total care and concern she represented a medical miracle. The doc-

tors couldn't believe the change. And now those dingbats have taken her away, maybe to die."

This attitude and feeling of personal involvement with the children is deeply felt by many Synanon members. The children in effect seem to represent the unfilled hopes and dreams of the adults. The elders of Synanon appear to enjoy watching the natural growth and miraculous development of children. They believe the school is an environment where the impediments to learning and growth seem to be less evident than in the general public school situation.

### Basic Social-Psychological Forces

The Synanon experience has some characteristics which are especially "therapeutic" for the former drug abuser. These are summarized by the following dimensions of Synanon.

*Involvement.* Initially, the Synanon society is able to involve and control the newcomer. This is, in part, accomplished by providing an interesting social setting made up of understanding associates who will not be out-manuevered by the addict's manipulative behavior. In Synanon, he finds a new society. He encounters understanding and affection from many people who have had life experiences similar to his own. He finds a community with whom he can identify, toward whom he can express the best human emotions that are in him, rather than the worst. He finds friends who will "pull him up" when he begins to slip or fall short of what he has set out to do: to develop and mature.

*An Achievable Status System.* Within the context of this system, the newcomer can (perhaps for the first time) see a realistic possibility for legitimate achievement and prestige. Synanon provides a rational and attainable opportunity structure for all members. For example, the current president of Synanon is an ex-addict who came to Synanon over ten years ago.

*New Social Role.* Being a Synanist is a new social role that can be occupied in the process of social growth and development. Many members decide to make Synanon their life's work. This new role is a legitimate one, supported by the ex-offender's own community. With the opening of new Synanon houses, the building of a Synanon city and the development of new projects, people with a knowledge of the Synanon dynamics are increasingly in demand.

(Many "splitees" from Synanon have been employed by other public "rehabilitation agencies," especially in New York City.)

*Flexibility and Social Change.* One of the most disconcerting aspects of Synanon for many newcomers is the seemingly arbitrary way in which older procedures, policies, attitudes, or life styles are continually overthrown by new ones. One of the personality criteria for adequately functioning at Synanon is the ability to tolerate ambiguity and rapid social change. Flexibility and change are key factors in the Synanon life style. Synanon's emphasis on rapid change seems to help people maintain interest, lends an intensity to life and helps to fight one of man's deadliest enemies, boredom.

Little reward is given for resting on one's laurels. A common response in Synanon to a person recounting past performances is, "Yeah, but what have you done for us lately?" The dynamic of rapid change assures a permanent antidote to rigidity, the cause of morbidity in most institutions and life styles. This aspect of Synanon change was expressed many years ago by Martin Luther but could just as easily have been said by the founder of Synanon: "Proficere est nihil aliud nisi semper incipere—to do enough means nothing else than always to begin again."

*Social Growth.* In the process of acquiring legitimate social status in Synanon, the ex-addict necessarily, as a side effect, develops the ability to relate, communicate and work with others. The values of truth, honesty and industry become necessary means for the goal of status achievement in Synanon. After a sufficient amount of practice and time, the individual socialized in this way reacts according to these values naturally in his every day life situation.

The principle of practicing an unfamiliar pattern is known at Synanon to "act as if." It means simply that even though the individual feels like a child and has urges to act out, if he acts or behaves as if he were already an adult, eventually the feelings will catch up with the "as if" behavior. The constructive behavior receives continuing reinforcement from the Synanon environment. The concept of "good" behavior preceding emotional change falls closer to behaviorism and the so-called "here and now therapies" than to classical psychoanalytic theory.

*Social Control.* The control of deviance is a by-product of the individual's status seeking.



Conformity to the norms is necessary in order to achieve. Anomie, the dislocation of goals and means, is a minimal condition in Synanon. The norms are valid and adhered to within this social system, since the means are available for legitimate goal attainment.

Ultimately, external control systems have their limitations and must, if they are to be maturational, be incorporated into an internal psychic structure. It is the functional absence of a reasonable superego that characterizes the psychopath. It is not unusual to see a newcomer addict, through identification with Synanon norms, engage in an orgy of self condemnation expressing unbearable feelings of guilt seemingly inappropriate to the nature of the offense. This often alternates with attitudes of extreme self righteousness and anger directed at other Synanon "deviates." This individual is often characterized as a Synanon fanatic or a "Nazi" by his colleagues who recognize that with further growth and maturation he will find it easier to control his acting out impulses and be less hard on himself. Along with this seems to come tolerance and empathy for others in this same plight.

*Empathy and Self Identify.* The constant self assessment required in his daily life and in the Synanon games fosters the consolidation of identity and empathy. The individual's self estimation is under constant assessment by relevant others, who become sensitive to and concerned about him. The process provides the opportunity for the individual almost literally to see himself as others do. He is also compelled as part of this process to develop the ability to identify with and understand others. A side effect is the development of self growth, social awareness, the ability to communicate, and empathetic effectiveness.

## Concluding Summary

In the early years, Synanon was almost exclusively devoted to the most recalcitrant criminal heroin addicts. In recent years, it has emerged as a new drug-free life style that has involved thousands of people, both young and old, many of whom were not themselves addicted to drugs. The current organization is administered by a combination of ex-addicts and involved citizens.

In summary, some of the more recent activities of Synanon include: (1) regularly attended Synanon game group interaction sessions; (2) a challenging and involving educational system; (3) business activities which help finance the operation; (4) a human research and development center at Tomales Bay, California, where plans are being constructed for a model city;<sup>4</sup> (5) a black social, cultural and educational program that has resulted in one of the best integrated social organizations in the country; (6) a special and effective group program for the parents of residents, and (7) a continuing series of innovative marathon (some 24 and 48 hour) educational and emotional experiences that have produced remarkably positive results.

The 1970s will no doubt prove to be an exciting decade for the development and fruition of many of the minor and major projects of the overall Synanon organization. As a side effect and consequence of Synanon's interesting and exciting life style, it can be predicted that several thousand drug abusers who join the organization will stop using dangerous drugs; and through their intense participation in this new life style, they will become valuable and productive citizens in the larger society.

<sup>4</sup>At this time, the U.S. Department of Housing and Urban Development is reviewing a proposal for developing a model Synanon city in Tomales Bay, California. This program could serve as a model experiment for helping to resolve the drug problem.

# The Pharmacist and the Physician

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IT IS WELL-NIGH IMPOSSIBLE to read any of the professional literature today without running across some allusion to "the health manpower crisis." This term, now being used so freely, is defined as "a stage in the sequence of events, at which the trend of all future events, especially for better or worse, is determined."<sup>1</sup>

Although almost everyone is willing to admit we have a health manpower crisis, most professionals are inclined to solve it with mild palliative treatment, rigorously insisting meanwhile on their own professional prerogatives.

A noteworthy example is the usual fashion in which physicians deal with what they have in the past referred to as the paramedical professions, but now—in deference to the sensibilities of the individuals concerned—they choose to call the allied health professions. Article after article has been devoted to the need of additional assistance for the physician. Recently, the American Medical Association went to the extreme of telling the profession of nursing what its future professional role should be.<sup>2</sup> Last September, writing in *CALIFORNIA MEDICINE*, Dr. Rheba de Tornyay, of the UC School of Nursing in San Francisco, explained why nursing did not take kindly to this sort of direction and how nurses themselves view their future professional roles.<sup>2</sup>

Another example has come from the discovery that allied health professionals can be of substantial financial assistance to the physician. At a recent seminar, it was noted that the group practice of medicine enables the physician to see

fewer patients per week and yet make as much money as he does in solo practice—and possibly more. Responsible for this phenomenon is the fact that the physician makes great use of allied health professionals as technicians. The situation has been summarized by a leading medical educator and administrator as follows: "Previously, we have also tended to consign other health workers to a kind of nonprofessional limbo, regarding them as workers for us rather than for the patient."<sup>3</sup> Such an arrangement may be beneficial to the income of the physician, and to his ego satisfaction, but it also has disadvantages which are becoming more clearly evident.

This approach once seemed well and good. It may even be acceptable today to the individual defined by Dr. Charles Reich as the Consciousness II American<sup>4</sup>—the individual who is a firm believer in the corporate state, in authority, and in working for the common weal.\* He, undoubtedly, is pleased to be part of a group practice in which he performs a certain number of B.U.N.'s per day, thereby making his contribution to "stamping out disease." He may not be too upset to realize that the physician is making most of the money and getting essentially all the credit.

The Consciousness II American, however, is being elbowed aside with great rapidity by Reich's Consciousness III American. The latter is far less willing to submit to an "unlived life" and rejects work which he finds boring or irrelevant. Increasingly, he is more interested in ego fulfillment than in mere economic betterment. For example, General Motors occasionally has

<sup>1</sup>The author is Dean, School of Pharmacy, University of California, San Francisco.

<sup>2</sup>Submitted February 3, 1971.

<sup>3</sup>Reprint requests to: Dean's Office, School of Pharmacy, University of California, San Francisco, San Francisco, Ca. 94122.

<sup>4</sup>See editorial, "Of Pharmacists, Physicians and Health Care," in this issue.



to shut down its assembly lines because a third or more of the workers decide not to bother to show up for work on a given shift. It is fascinating to observe that not only has our society made it possible for people to make such choices, but also that, more and more, they are electing to do so.

It is ironic that now, when industry and our corporate state are being forced to face the difficulties of the production-line approach, medicine is attempting to adopt it. The features of multiphasic screening, assembly-line therapy, and computer-based medicine may be appealing to some health planners, but these features appear to be less acceptable to the patients being treated and to the people running the machinery. I believe such an approach is doomed to failure, and should be aborted now while still in the early stages.

Many of the difficulties which bedevil inter-professional cooperation may be illustrated at the physician-pharmacist interface. At the national level, organized medicine consistently compliments members of my profession, using such pleasant but timeworn phrases as "valued members of the health care team." It is apparent to all of us, however, that this is mere rhetoric—a fact made startlingly evident by the almost paranoid reaction of much of organized medicine to the proposed challenge of existing anti-substitution laws now being considered by pharmacy organizations. Indeed, this sort of reaction has been the rule rather than the exception in pharmacist-physician interactions.

## The Pharmacist of the Future

My generation of pharmacists (composed almost entirely of Consciousness II Americans) was generally willing to accept a "back-of-the-bus" status. The Consciousness III American is not.

Accordingly, I believe that the future of health care in California, and in fact throughout the nation, depends upon better communications among all the members of the so-called health care team, and that dictation—which generally seems to be delivered from on high—is not going to be successful. I should like, therefore, to put forward my ideas of a viable role for the pharmacist of the future—a role which is complementary to that of the physician, and yet will provide adequate ego satisfaction for both phar-

macist and physician, while simultaneously leading us toward our professed goal of better patient care.

Perhaps it is well to remember that, at one time, the apothecary played the part of "physician to the poor." Later, as the preparation of medications became more complex and difficult, and the rewards of shopkeeping more appealing, the pharmacist turned away from this role, adopting more and more that of combination merchant-and-chemist. After World War II, as the need for compounding medications on the premises became less important, he found himself increasingly estranged from the widely publicized but barely existent "health care team."

This estrangement was worsened by the discovery that what is good for the Pharmaceutical Manufacturers Association is not necessarily good for the pharmacist, and that his fellow professional—the physician, whom he held in such high regard—was quite capable of responding to the public outcry against the high cost of medical care by putting most of the blame on the pharmacist.

At the same time, the literal deluge of new pharmaceutical products required the pharmacist to carry an increasingly larger and more expensive inventory, much of it repetitious. The pressures of third-party payors, along with those from the general public for more economical medical care, reduced the profitability of his entire operation to a level far below that achieved by drug manufacturers.<sup>5</sup> Simultaneously, this plethora of new drugs was causing serious problems for the physicians, and iatrogenic disorders had become preponderantly drug-induced disorders.

## The Drug-Induced Disorders

Dr. Henry E. Simmons, director for the Bureau of Drugs in the Food and Drug Administration, described the situation last September in these words:

"It is clear to me that the increasing misuse of drugs in America poses a major problem to us all. I would like to consider with you some of the dimensions of the problem. The information on this is sketchy, but rough figures are available. First of all, the American people are being dosed with approximately two billion prescriptions per year. This excludes the use of

over-the-counter drugs, which, as you know, is even greater. It is common knowledge that much drug therapy avails little or nothing in terms of patient benefit and that a large number of these prescriptions have been for ineffective or only partially effective drugs. In fact, Americans spend nearly a half billion dollars a year for prescription drugs for which there is at present no valid proof of efficacy. Unfortunately, whether a drug is effective or ineffective, it can still cause adverse reactions and not infrequently, does. It appears that the incidence of complications in drug therapy is roughly 10 per cent, and that approximately 5 percent of patients admitted to the medical services of general hospitals are admitted because of serious drug reactions. It is estimated that approximately one and a half million hospital admissions per year are necessitated by the diseases caused by drugs. After admission into the hospital for whatever reason, the hospitalized patient faces a 10 to 20 percent error rate in the drugs which he receives. In addition to that, far too many drugs are prescribed by at least some physicians. Numerous studies have shown that the average hospitalized patient received approximately ten drugs per hospitalization and not infrequently up to 30 drugs. Certain drugs are used inappropriately and you are all aware of the widespread misuse of chloramphenicol and other antibiotics. In addition, there are other examples such as the use of combinations of thyroid, Dexedrine, diuretics and digitalis for obesity from which a number of deaths have resulted. Also there is an extraordinary variation in the way doctors treat patients with the same disease depending on which region in which the patient might find himself. This is not only difficult to explain, it is difficult to defend. The formulations of many commonly used combination drugs are not rational as fixed combinations, and make it virtually impossible to practice good therapeutics. In spite of this, approximately 40 percent of the best selling drugs in America are fixed combinations."<sup>6</sup>

At the Los Angeles County-University of Southern California Medical Center, Dr. Robert Maronde and his associates have added forbidding documentation to such comments on irrational prescribing. In a study of some 52,000 consecutive prescriptions, representing the 78 products most frequently prescribed for outpatients, they found nearly 7,000 that called for

drug amounts in what were clearly grossly excessive quantities. Among the examples were single prescriptions calling, respectively, for 800 capsules of chlorthalidone, 800 tablets of methyl-dopa, and 2,000 tablets of furosemide.

One patient, Dr. Maronde reported, received 54 prescriptions over a 112-day period, including 12 individual prescriptions on one day, and 11 on another. "He received during this time 1,130 capsules of propoxyphene, 870 capsules of chlorthalidone, 700 capsules of diphenylhydantoin, 620 capsules of griseofulvin, 520 tablets of sodium salicylate, 500 tablets of phenobarbital, 500 tablets of nitroglycerine, 300 tablets of thyroid, 300 tablets of multiple vitamins, 300 tablets of furosemide, 300 tablets of acetaminophen, 240 tablets of triamcinalone, 230 tablets of hydrochlorothiazide, 200 tablets of phenobarbital-ephedrine-theophylline, 200 tablets of digitalis, 200 tablets of probenecid, 200 tablets of acetylsalicylic acid, 40 tablets of sulfamethoxazole, 40 tablets of chlorpromazine, and 26 tablets of aluminum hydroxide-magnesium hydroxide gel."<sup>7</sup>

### The Prescribing Pattern of Physicians

In its historic reports, in 1968 and 1969, the HEW Task Force on Prescription Drugs surveyed the prescribing patterns of physicians.

"We find that few practicing physicians seem inclined to voice any questions of their competency in this field of therapeutic judgments," the Task Force stated. "We also find, however, that the ability of an individual physician to make sound judgments under quite confusing conditions is now a matter of serious concern to leading clinicians, scientists, and medical educators."<sup>8</sup>

Among the factors contributing to the problem, the Task Force said, were these:

- Inadequate training in the clinical applications of drug knowledge during the undergraduate medical curriculum.
- Inadequate sources of objective information about drug properties and indications available to practicing physicians.
- Widespread reliance by prescribers for their continuing education upon advertising and promotional materials distributed by drug manufacturers.
- Exceedingly rapid turnover in the popularity of prescription drug specialties.
- The limited time available to practicing



physicians to examine, evaluate, and maintain currency with the therapeutic claims for newly marketed products.

Dr. Harry F. Dowling, formerly chairman of the Department of Medicine at the University of Illinois, presented this summary: "The few studies that have been made on how doctors use drugs show that (1) sources of information from the drug industry appear to rule the doctor's actions as much as those coming from his colleagues, and (2) a substantial proportion of doctors practice poor therapeutics, by any reasonable standard . . ."<sup>9</sup>

The problem of achieving rational therapeutics is both real and severe, and no panacea is readily available. Many have looked to the establishment of divisions of clinical pharmacology in every medical school as the cure for the ailment. The recognition of this new discipline, and the consequent increased emphasis on therapeutics in medical curricula, will undoubtedly have a healthy effect upon future practitioners. Moreover, clinical pharmacologists, working as medical investigators, will help to solve many currently baffling aspects of therapeutics. But it seems unlikely that the physician of the future will have the time or the inclination to devote the effort needed to maintain his therapeutic knowledge at the same high level which peer review and self-respect demand of his diagnostic competency.

### The Pharmacist and the Therapeutic Regimen

Thus, I propose that physicians should start thinking of the pharmacist as a colleague vitally interested in the therapeutic regimen of the patient. This is not to suggest that the pharmacist take over therapeutic management, but rather that he work with the physician cooperatively to ensure the best possible therapy for the individual patient.

Obviously, this interaction will have to take place in all the different settings in which patients receive care. In the institutional setting, for example, the pharmacist must participate in patient rounds and become familiar with the problems of all patients in his section. Here the need is essentially to make the pharmacist intimately concerned with the physician or dentist regarding the curing function, and with the nurse regarding the caring function.<sup>10</sup> Already a number of hospitals through-

out the United States are engaged in experimental projects which utilize the pharmacist in such fashion. The results to date are most encouraging, but definitive studies, including those on cost effectiveness, are not yet complete.<sup>11,12</sup>

Perhaps of even more interest to the readers of a medical journal is the potential utilization of the pharmacist in ambulatory care. Many pharmacists have already undertaken the responsibility of keeping family medication records; these enable the pharmacist to alert the physician when he has unwittingly prescribed a drug which is contraindicated because of other medication currently being taken by the patient, perhaps prescribed by another physician. In addition, the pharmacist is also generally aware of the over-the-counter drugs with which the patient may be dosing himself.

In individual cases, where mutual trust and respect had been established, it would certainly seem logical to give the pharmacist responsibility for monitoring the drug regimen.

The physician might well allow the pharmacist to select the source of a prescribed drug product—a responsibility which he already carries in many hospital centers. Unquestionably, cost must be an important consideration—second only to the clinical welfare of the patient—in every step of health care delivery, and the pharmacist should assume appropriate authority for this aspect of drug therapy.

Physician-pharmacist cooperation can improve the patient's therapy and, in many cases, hold costs to a reasonable level. This approach is often decried, at least in theory, as antithetical to "the physician's free right of choice." Such a charge may or may not be valid in theory, but the results of practical application have generally been satisfactory. Where physicians and pharmacists have worked together to establish guidelines and methods, their cooperative efforts appear to be successful.<sup>13</sup>

The American Pharmaceutical Association is developing a model agreement for use by physicians in authorizing a pharmacist to choose the source of drugs dispensed when the physician prescribes by brand name, thereby circumventing the anti-substitution law. (Such an agreement has been successfully in effect for many years in many leading hospitals and drug insurance or health prepayment plans.) It is probable that many California physicians will be asked to participate in

an agreement of this kind, and it would be worthwhile for them to give the proposal their serious consideration.

### Differing Views of the Pharmacist's Role

Innovative medical educators, such as Dr. Edmund Pellegrino, Dean of the School of Medicine at the State University of New York at Stonybrook, have suggested a number of additional tasks for the pharmacist in an emergent health care system, with a role as a drug information expert for pharmacists in each center for primary, secondary, and tertiary care.<sup>14</sup> Others, such as Dr. Robert Ebert, Dean of the Harvard School of Medicine, have suggested important roles for the pharmacist more closely related to the present health care systems.<sup>15</sup>

In contrast, Dr. Dwight L. Wilbur, former president of the AMA, has suggested: "It is the feeling of the AMA, and my feeling, that pharmacists . . . can play a larger role in the health team by accepting more responsibility as pharmacists—rather than by trying to make themselves therapeutic consultants to physicians."<sup>16</sup> More recently, the Indiana State Medical Association scoffed at the idea of the pharmacist providing advice on drugs to the physician, seeing the pharmacist as threatening to switch from his traditional role as "an expert on pharmacology" to that of an "interloper in therapy."<sup>17</sup> In this connection, it should also be noted that many pharmacists view with trepidation the prospect of playing any meaningful role in therapy.

Nevertheless, the fact remains not simply that the physician-pharmacist interface is marked with fear, hostility, suspicion and fractured egos, but that there is an undeniable need to improve drug therapy for the patient. In the long run, what matters is not interprofessional disagreements, but patient welfare. As one major step in achieving better, more rational drug treatment, there is an urgent necessity for better communications between the physician and the pharmacist. It is

time that our professions start meaningful communications and, in the jargon of youth, "telling it like it is."

There is no doubt that our professions sincerely want to provide the best possible health care for all Californians. Similarly, there can be no doubt that the only way of achieving this goal is by working in concert. If a manpower crisis is indeed upon us, as the leaders of medicine have emphatically declared, then it is imperative that we all must discuss, plan, test and eventually implement new approaches to the delivery of health care.

Without that cooperation between all of the health professions, the probability of Californians receiving the quality of medical care they deserve is indeed bleak. With such cooperation, we may be able to provide it.

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# LETTERS *to the Editor*

## Chemotherapy of Amebiasis

*To the Editor:* It is interesting to witness a revival of concern over amebiasis. The discussion by Barrett-Connor (Calif Med 114:1-6, Mar 1971), and the symposium by Turner, Lewis, Hayes and Ziment (Calif Med 114:44-55, Mar 1971) deserve more comment than I am qualified to give. But I am able to say something pertinent about the chemotherapy of this widespread infestation.

As we showed some forty years ago (JAMA, 98:195-198, 1932; 100:1658-1661, 1933), 5-chloro-7-iodo-8-hydroxyquinoline was found to be the most satisfactory amebicide of some dozen halogenated quinolines studied. This is readily available as "Vioform." 5-7-diiodo-8-hydroxyquinoline, or diiodohydroxyquin, is about as effective, but it is twice as costly, since it contains twice as much iodine. Iodine is by no means inexpensive.

Since then, Vioform has been found the world over to be useful in clearing the intestinal tract of many parasitic and bacterial invaders. It is practically non-toxic, since it is neither soluble in nor absorbed from the gut. It is effective in doses of 250 mg thrice daily for ten days, with such a course of treatment repeated after a ten-day rest period. Vioform is as effective in symptomatic intestinal infection as in asymptomatic conditions. If motile forms are present, Vioform may be dusted into the rectum and lower bowel by insufflation.

Emetine should be reserved for amebic abscess. It should be remembered that cardiopathies may be expected from a course of emetine therapy sufficient to be effective (Arch Path 11: 546-553, 1931).

If cachexia is present, it might be wise to recall carbarsone, 4-carbamino-phenyl-arsonic acid (JAMA, 98:189-194, 1932). This has a tonic effect in addition to its effect in removing amebic cysts. It is usually effective in a dose of 250 mg thrice daily for ten days, and it may be given in an enema to remove motile forms from the lower bowel. It is partially absorbed, but 95 percent of what may be absorbed is excreted in the urine within 24 hours. It should not be used if there is renal involvement of any sort.

It does not seem that antibiotics, metronidazole or niridazole have any special advantage over older, well-used drugs in treating amebiasis. They are generally more expensive. My colleagues in studying the chemotherapy of amebiasis were Hamilton H. Anderson and Norman David.

CHAUNCEY D. LEAKE  
*University of California, San Francisco*

## Metachronous Development of Regional Enteritis of the Colon in a Patient with Ulcerative Colitis

*To the Editor:* I would like to comment on the paper by Drs. Babb and Kieraldo on "Metachronous Development of Regional Enteritis of the Colon in a Patient with Ulcerative Colitis," published in the March, 1971 issue of CALIFORNIA MEDICINE. (pp 80-84)

The authors point out that it may be impossible to classify certain patients with inflammatory bowel disease into the distinct categories of ulcerative colitis or regional enteritis and quote pertinent literature on this now well-accepted fact. Their case is a good example demonstrating this difficulty in classification. The title of their paper, however, and the conclusion of an "apparent progression of one disease into the other" do not appear justified based on the pathologic findings presented. The caption on Figure 1, from the original rectal biopsy, refers to a "crypt abscess" which is not demonstrated. Similarly, Figure 4, representing the later biopsy shows indeed trans-

mural and serosal inflammation consistent with regional enteritis. The illustration, however, does not include submucosal tissues as referred to in the caption and the text indicates that granulomata were not present. Since neither biopsy was entirely characteristic for either ulcerative colitis or regional enteritis, the conclusions reached cannot be considered as being substantiated.

WILLIAM H. KERN, M.D.

*Chairman  
Department of Pathology  
The Hospital of the Good  
Samaritan Medical Center  
Los Angeles*

## The Authors Reply

*To the Editor:* It is difficult to judge biopsy material on the basis of reproduced photomicrographs. The biopsies have been reviewed with two pathologists, and we are in complete agreement that they show exactly those findings stated in our report, including features disputed by Doctor Kern. Figure 1 shows a crypt abscess, and Figure 4 shows submucosal tissue. We feel our conclusions are substantiated.

RICHARD R. BABB, M.D.

JOHN H. KIERALDO, M.D.  
*Palo Alto Medical Clinic*

## BLOOD GASTRIN DETERMINATION BY RADIOIMMUNOASSAY

"A very exciting advance in the field of gastric physiology and disease has occurred in the last year—the development of an accurate radioimmunoassay technique for the measurement of gastrin in biological fluids and tissues . . . . This technical achievement has made it possible to study the site of origin of the hormone gastrin, its metabolism, the role of gastrin output in digestion, and the blood level of gastrin in disease. It has been shown . . . that blood gastrin levels in man are elevated in conditions associated with end-organ failure, such as pernicious anemia and gastric cancer and that the gastrin levels increase with age. Furthermore it has been demonstrated by a number of workers that the Zollinger-Ellison syndrome is consistently accompanied by markedly elevated blood gastrin levels so that the measurement of gastrin in peripheral blood has become the best method of diagnosing this syndrome."

—MARSHALL J. ORLOFF, M.D., San Diego  
Extracted from *Audio-Digest Surgery*, Vol. 16, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057



## Arbitration

JAMES E. LUDLAM, ESQ., *Los Angeles*, AND HOWARD HASSARD, ESQ., *San Francisco*

FOR TWO YEARS a group of Southern California hospitals and attending physicians has been involved in an experimental program intended to explore arbitration as an alternative to court litigation of claims, including malpractice claims.

Because of the nature of such claims, considerable time must elapse from the inception of the program before a valid body of experience can develop. However, due to widespread interest in the demonstration project, this article has been prepared to report events thus far and to explain the project and goals it is designed to achieve. In its final design the project incorporated the thinking of nearly 100 persons and organizations.

Unique to this project is the inclusion of the agreement to arbitrate in the Conditions of Admission form signed by the patient at the time of admission to the hospital. As will be shown later, a legal question of basic importance to arbitration is involved. The idea came to one of the authors (J.E.L.) following a meeting of the California Hospital Association's group professional liability program. One of the principal issues discussed was the long delay in determining actual losses for any claims year. The fact that an insurance company may be collecting premiums based on current dollars and paying judgments inflated by the passage of time many years later has been a major deterrent to additional carriers who might otherwise enter the field. Concern about the high costs of professional liability insurance also has made the idea of arbitration seem attractive.

Before practical questions could be faced, the

basic legal issues had to be resolved. The first issue was whether a form of agreement that would be mutually binding upon the patient on the one hand and the hospital and attending physician on the other could be developed.

There is a legal doctrine called "adhesion" which holds that an agreement executed when one party is placed in an ineffective bargaining position may not be binding upon that party if the court finds any element of unfairness or overreaching by the party who originally prepared the agreement. The doctrine of adhesion would appear to apply to any statement signed by a patient at a hospital. The California Supreme Court has stated this succinctly: "The admission room of a hospital contains no bargaining table . . ."—*Tunkl v. Regents of University of California*, 60 Cal. 2d 92 (1963).

Since the *Tunkl* case involved a paragraph in the Conditions of Admission form that required the patient to waive any right to claim negligence against the hospital, the question of bargaining power and fairness was a critical issue in the court's decision. It is apparent that a court will examine carefully the fairness of any agreement to arbitrate executed by a person who is given the alternative of signing it or not being admitted to the hospital.

On the other hand, courts view the use of arbitration as an alternative method of settling a legal dispute as good public policy. The California Supreme Court case of *Doyle v. Giuliani*, 62 Cal. 2d 606 (1965), involving a challenge to an arbitration clause contained in a subscriber agreement of the health insurance program of the Ross-Loos medical group,\* is particularly important. In this

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Reprint requests to: California Medical Association, 693 Sutter St., San Francisco, Ca. 94102 (Mr. J. E. Curley, Jr.).

\*The Ross-Loos medical group is a closed panel medical insurance program similar to the Kaiser-Permanente Plan except that it is not hospital-based.

case, the claimant was a minor who enjoyed dependent coverage under his father's policy. The California Supreme Court not only bound the child to the contract executed by his parent, but also approved of the use of arbitration for settling such a dispute by stating: "The arbitration provision in such contracts is a reasonable restriction, for it does no more than specify a forum for settlement of disputes." Although the situation of an applicant for health insurance differs somewhat from that of a patient in the admission room, the Ross-Loos case did satisfy the public policy question as to the use of arbitration.

### Solving Adhesion

To solve the adhesion problem a two-step approach that is not only fair and equitable but also should be legally binding was used. First, the patient is given the right to delete the arbitration clause in the Conditions of Admission form simply by placing his initials in a box directly beneath the arbitration clause. Admission clerks are instructed to accept such deletion without question, so the element of compulsion is eliminated. Second, the patient can delete the arbitration clause by written notification within 30 days after his discharge. California procedure specifies that the patient or his representative be given a copy of the signed Conditions of Admission form. If for any reason the patient merely scanned the form or did not understand it fully, he has a reasonable time to study his copy. If he then fails to repudiate it, he is bound by its terms. The period of 30 days was considered a fair and adequate time for the patient to study his copy of the Conditions of Admission Agreement.

After these basic issues were resolved, legal counsel for the California Hospital Association (CHA) then contacted the California Medical Association (CMA) and the principal insurance carriers for physicians and hospitals in the area to obtain their reactions, questions, and suggestions. The project was now officially a joint undertaking of CHA and CMA. A preliminary decision was made to use the American Arbitration Association (AAA) as an impartial body to administer the program. Several possible arbitration procedures exist under California law. The most common procedure specifies that each party select an arbitrator; if the arbitrators cannot agree, they select a third whose decision is binding. This too much resembled a

### DISCOVERY

In November, 1970, a proposal to give the same rights to discovery in an arbitration proceeding involving personal injury as in court became effective under California law. Discovery is the exchange of information by the involved parties before the hearing or trial, making use of procedures defined by statute. Discovery is based on the theory that a lawsuit should be a "search for the truth" and "not a game" to be fought and won mainly by strategic moves and surprise tactics. Attempts to thwart discovery are subject to perjury penalties. Included in discovery are rights to depositions, mental and physical examinations, examination of records and "things."

negotiated settlement. The American Arbitration Association system was chosen because it is designed to reach a clear-cut decision of right or wrong.

The AAA arbitration process differs in certain important details from the standard form of arbitration established by state laws. Under AAA procedures the arbitration process is initiated with the filing of a written demand for arbitration with the local office of the AAA. At this point the AAA staff member assumes complete responsibility for the administration of the case, including assisting both sides in procedural matters, until the award is rendered. Upon receipt of the demand for arbitration, the local AAA administrator sends identical lists containing the names of technically qualified arbitrators to both sides, who then have a period of seven days in which to object to any of the arbitrators on the list and to number the remaining ones in order of preference. The lists are matched to make the final selection; if there is no matching, an additional list is submitted to both sides. The hearing is conducted in a manner somewhat similar to that of a court hearing, but with a degree of informality that expedites the process. The arbitrators are not required to follow strict rules of evidence, but may hear all evidence that has a bearing on the controversy. A decision must be made within 30 days of the conclusion of the hearing. Except in extraordinary circumstances, the decision is final.



Even when there has been previous agreement to arbitrate, the use of arbitration is not mandatory unless one of the parties elects to initiate the arbitration process, at which time it does become binding. It was recognized that some cases can be handled more appropriately in the courts than in arbitration. Moreover, only those physicians who have agreed in writing to arbitrate are bound, and no consulting physician can initiate arbitration without the participation of the admitting physician. If a physician's insurance carrier refused to cooperate, the case will be tried separately in a court of law.

The principal insurance carriers for most of the physicians and hospitals who requested participation in the project cooperated fully. Without their approval, there would have been serious question whether the use of an arbitration clause by a physician or a hospital would trigger the non-cooperation clause in the insurance policy.

### The Demonstration Project

The demonstration project is limited to nine hospitals in a restricted geographic area. Originally eight hospitals introduced a new Conditions of Admission form containing an arbitration clause on July 1, 1969. They were California Hospital, Los Angeles; Daniel Freeman Memorial Hospital, Inglewood; Garfield Hospital, Monterey Park; Holy Cross Hospital, San Fernando; Hospital of the Good Samaritan, Los Angeles; Long Beach Community Hospital, Long Beach; Memorial Hospital of Glendale, Glendale; and South Bay Hospital, Redondo Beach. On July 1, 1970, St. Joseph Hospital, Orange, and Children's Hospital of Orange County, Orange, joined the pilot project. On February 9, 1971, Holy Cross Hospital closed due to severe earthquake damage.

For each hospital, participation was approved by the governing board, the executive medical board, the insurance carrier for the hospital, the insurance carriers for the majority of the physicians on the staff, by a substantial majority of the members of the active medical staff, and by a joint committee of the California Hospital Association and the California Medical Association.

The open sessions at which the project was explained to the hospital medical staffs were most stimulating, and as a result a number of constructive changes were made. Of great importance to the physicians was the fact that the decision of a

hospital to participate in the project did not bind individual members of the medical staff to participation. Each physician received a card on which he indicated his decision to participate or not to participate. Physicians responsible for the admission of 80 percent of the patients in the demonstration hospitals elected to participate in the plan, and the figure has risen to more than 90 percent in most of the hospitals.

### Goals of Arbitration

Presentations to medical staffs stressed the goals of the arbitration project:

- To speed the handling of claims so that they can be disposed of in months rather than years.
- To reduce substantially the time a physician must spend in litigation.
- To save the time of physicians, witnesses, and lawyers.
- To ensure a high degree of sophistication in the decision-making process.
- To minimize unnecessary appeals because of the recognized finality of an arbitration award.
- To limit publicity because of the confidential nature of the arbitration process as contrasted with the flamboyant aspects of many jury trials.
- To limit the amount of judgments, which otherwise may be too large because of emotional and theatrical appeals to a jury.

### Progress

Twelve months after initiation of the program in the original eight institutions, a progress meeting was held with representatives of the participating hospitals. In the first 12 months, only about 50 persons of the more than 70,000 admitted to the hospitals chose to reject arbitration, including three who did so by written notice during the 30-day period after discharge.

At that time, no suits or requests for arbitration had been received. This was not surprising, because claims or suits generally follow in from six to twelve months after the patient's admission at the very earliest. All participating hospitals expressed a desire to continue in the project and indicated widespread support from members of their medical staffs.

Through December of 1970 there had been 124,758 admissions under the project and 116 rejections of the arbitration option, of which 113 were made in the hospital and three by written

notice after the patients left the hospital. There were still no suits filed as of that date.

This project is but one of a series of major programs designed to allay the increasing costs of professional liability insurance. The California Hospital Association and the California Medical Association will continue to stress prevention of conditions giving rise to causes of action and will work for legislation that will restore reasonable

protection to defendant physicians and hospitals from unlimited extension of the doctrine of *res ipsa loquitur* and from an ineffective statute of limitations.

Copies of the Hospital Arbitration Regulations developed in cooperation with the American Arbitration Association are available from James E. Ludlam, Musick, Peeler & Garrett, One Wilshire Boulevard, Los Angeles, California, 90017.

#### **"PRE-HERNIA" IN PRE-EMPLOYMENT EXAMINATION**

Do you recognize an incipient or industrial hernia on pre-employment examination?

"I think that the so-called 'pre-hernia' is one of the most annoying things we face. I have what I might call minimum standards, that is, either it is a hernia or it isn't. In my way of looking at it, a hernia is an abnormal protrusion of a viscus through an aperture in the body parietes. Some patients have a large dilated ring; they have a rotund abdomen; and if you get your finger through the ring, you can palpate the floor of Hesselbach's triangle. That, in my opinion, is not a hernia, and I don't recommend repair of it. Furthermore I don't make a diagnosis of pre-hernia because once you use the word hernia in the presence of a patient or in one of those industrial cases you've had it. The patient becomes totally incapacitated. Yet we know that a small direct inguinal hernia is a very insignificant threat. So I have my minimum standards. If it doesn't come through the external ring, I do not call it a hernia; and in my practice I do not recognize the so-called pre-hernia."

—JOSEPH L. PONKA, M.D., Detroit

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# Computer Applications in Health Services

A Socio-Economic Report of the Bureau of Research and Planning,  
California Medical Association

TWENTY-FIVE YEARS AGO, the computer had scarcely been dreamed of; today it is practically impossible for an urban American to pass a day without at least indirect contact with one. The role of the computer in recording the events of our lives, from birth to death, is already of primary importance. Among their other functions, computers are used in figuring income taxes, credit card use, consumption of materials, and for statistical analyses such as computing the cost of living index. This primary role of the computer, recording, has been extended into the entire health care industry, where it holds considerable promise. This *Socio-Economic Report*, in addition to bringing together information on recent computer advances in medicine, will elaborate on some current and future possibilities for computer applications in the health fields.

Before discussing these applications, however, a brief review of the functions and capabilities of the computer in general is in order. These basic functions are: (1) Data Input: The ability to translate data, from instruments or man, into computer language. (2) Data Processing: The manipulation of data to answer inquiries. (3) Information Output: The ability to provide processed data in usable form. (4) Communication and Transmission: The ability to transmit data from input-source to computer to output, regardless of location. (5) Reliability, with emphasis on speed and convenience of the system.<sup>1</sup> The potential applicability of such a system to a field where the amount of scientific knowledge has

approximately doubled *each decade* since 1900, is the subject of this *Report*.

It should be emphasized that references to specific systems in this *Report* do not imply their endorsement.

Currently, a major problem in the health care field is the lack of availability of medical services. To label this lack "the doctor shortage" is an over-simplification. A shortage of services usually provided by the physician does exist, but not all of these services necessarily require the skills of a physician. In the private practice setting, for example, many of the functions of the computer such as accounting and bookkeeping, which could serve to free the physician from time-consuming tasks, have been restricted by the high cost of such services. However, as these financial limitations are removed, and as the cost of labor rises, the need for better ways to meet increased demands on the patient care system can take precedence.<sup>2</sup>

Since traditional methods of data gathering and dispersal are becoming increasingly cumbersome, the expansion of the base of medical information must be viewed with computer support in mind. According to officials of IBM's Advanced Systems Development Division at Yorktown Heights, New York, the focus of research over the next ten years will be to: (1) use the computer to expedite the "total flow of information" going on within the hospital; and (2) expand the application of computers as therapeutic and diagnostic aids.<sup>3</sup>

While medical computer usage in the 1960's was largely concerned with superior record keep-

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ing and billing procedures, and with applications in research and education, the emphasis is currently changing to include more critical medical tasks. There is no question, experts maintain, that the computer is now relevant to four major concerns of medicine: office operations, patient care, medical research, and diagnosis and treatment planning. Insofar as these areas are separable, they will be individually discussed.

### Office Operation

Systemedics, one of various medical office systems available to physicians, provides a wide variety of office services. This system prepares each physician's statements or credit letters, detailing every charge or receipt; identifies the patient if more than one dependent visited the practice during the month; and, in the case of group practice, lists the physician who performed the treatment. Systemedics can segregate private insurance or Medicare charges and store them until treatment is completed, then retrieve the charges along with other pertinent stored claim data. A complete history with detailed charges is sent to the physician on a physician's service report which is acceptable to the majority of insurance carriers. Each month, a complete alphabetical listing of active accounts is provided showing billing charges, delinquency status, insurance activity, payment history, and the allowable figure for income tax deductions for each account.

The physician selects the period an account is to remain open; after that, a series of credit letters is sent automatically. The computer ages every account and tracks each delinquency. Also, each month the physician's accounts receivable are totalled, showing charges, receipts, amounts delinquent, growth development of the physician's practice, and other data pertinent to the management of the office. For partnership practices, each physician's production can be accurately totalled.

In an effort to speed and control the payment of medical bills for physicians, a unique new computerized system has been designed and developed by Blue Cross and Blue Shield of Virginia and Western Data Products of Los Angeles. This new system will allow a doctor to transmit a claim for service to Blue Cross and Blue Shield by means of a keyboard type terminal device in his own office. The data will be

transmitted into a data center; verification of the claim will be returned to the physician within seconds through an automated voice response. The claim will then be processed and a check issued. It is asserted that the advanced system will substantially reduce paper-work and administrative costs in the doctor's office, as well as prevent errors in the payment of claims.<sup>4</sup>

### Patient Care

During the initial phase of medical computing, many programs were set up to automate physicians' orders, laboratory reports, and other similar functions. These "first generation" systems provided clinical medicine with much needed experience in this new field, but for the most part these programs were not addressed to the task of uniting medicine with the new technology. The "second generation" programs, written during the past three or four years, have focused on clinical rather than clerical problems, and have brought computer usage into medical judgment and therapeutic decisions. Essentially, these programs attempt to establish organized data banks of one sort or another with clerical benefits a matter of secondary importance.

Second generation programs will necessitate the development of a full clinical system. When data from many patients are stored in a computer memory bank, imaginative organization of input, storage, and output is necessary for useful retrieval. To insure comparability of similar cases, rigid uniformity in the recording of data is imperative. Therefore, the first step toward establishing a useful data bank is the standardized input of all medical records. This standardization has been achieved by designing a set of prestructured records which can closely follow the working habits of the physician. Of course, these records must be computer-compatible.

It is important to keep in mind that the present commercially available computers are fully adequate for the operation of this type of data bank. Even the cost is not excessive when compared with inefficient manual methods. The present difficulty lies mainly in designing the full system, the medical input structure, and in training physicians to adjust to the system's technology.<sup>5</sup>

A computer system can provide the tools for more logical and efficient management of all aspects of information in the preservation of pa-



tient health and in the treatment of illness. The Yale Medical Computer Science Section, for example, is applying computers to the management of information in patient care. In developing automated systems for the collection and retrieval of medical histories, the Yale group is departing in emphasis from other systems by using computers and information science in research and teaching relevant to changing patient care needs. Medical decisions are simplified for the practitioner, for paramedical personnel, or for the computer if the right data are assembled in an orderly and logical fashion. A computer-aided medical history data bank will vastly improve the present diversified ways of assembling medical information. But the goal of more efficient medical information recording and retrieval will be worthwhile only if physician effort is spared by automation and increased use of paramedical personnel.<sup>6</sup>

Most experts believe that the hospital will probably remain the major point of contact between doctors and computers. The goal of current planning is a hospital information system capable of giving an instant report, containing every useful item of information about any given patient. The need for such a system is overwhelming, if only to keep track of all the data produced in a hospital. It has been estimated (by Melville H. Hodge, Assistant Director of Information Systems for Lockheed Missile and Space Corporation) that as much as 30 percent of all hospital costs go for manual information handling. And processing of a single laboratory test order may involve twelve written information transfers. For example, Boston's 1,000-bed Massachusetts General Hospital admits 30,000 patients annually, treats another 50,000 in its emergency rooms, and handles 125,000 outpatient visits. Every admission results in a flood of information to be sent to 66 different areas. The hospital's 24 laboratories perform one million procedures a year. Every day 4,000 calls are made for records; one in five of these records cannot be immediately located.<sup>7</sup>

The State University of New York's Downstate Medical Center in Brooklyn appears to have developed the most advanced hospital information system in use today. This computer has 49 teletypewriter stations, with nine more located at other hospitals in Brooklyn to form an emergency-bed-assignment system. Almost

every bed in Downstate's hospital is assigned by the computer. In assigning a bed to each entering patient, the computer is programmed to consider age, medical condition, and sex, among other factors.

The computer also handles laboratory, x-ray, drug, and other orders of a similar nature. The physician enters the request on the patient's chart in the usual way. An assistant then types out the order at the nearest computer terminal. In the case of a lab test, the technician who performs the test transmits the results back through the computer, which stores the data and bills the patient automatically.<sup>7</sup>

High cost will probably prevent all but the very largest hospitals from having their own computer systems. Therefore, Lockheed at Sunnyvale, California, recently proposed a Medical Information System which will link several hospitals to a centrally located electronic data processing system. The proposed system would have video screens placed at various points throughout a hospital. Access to the computer would be made through the video screen by means of a "light pen," which is used to write orders directly on the screen.

The proposed system would encompass doctors' orders, medications, pharmacy orders, nurses' instructions, periodic shift reports, and 24-hour summaries for each patient, making instantly available to the physician a complete status report on each patient. This system is specific enough for the needs of the physician, a quality lacking in other medical information systems.

The regional availability of the proposed system can produce substantial savings to hospitals, since each would not have to buy or lease its own high-priced computer hardware. Lockheed has designed a system which is extremely efficient and workable as presented. The major problem encountered in implementing the system would be in training medical personnel in the use of the computer and in orienting them toward electronic technology.

## Medical Research

The computer is an extremely powerful and versatile tool, adaptable to a wide range of tasks involving data acquisition, editing, and storage; information retrieval and display; complex mathematical computation and data reduction; and

information feedback and control. Therefore, the computer has great actual and potential applicability to research in medicine and, through progress in research, to increased quality of medical care.

Despite the computer's obvious potential, many biomedical scientists have for a number of reasons been reluctant to use electronic data processing. High costs have limited the amount of automatic data processing equipment available to the biomedical researcher. Also, there has been little variation in the types of equipment available; the new, small, highly flexible computers essential to clinical and laboratory research are of relatively recent design.

Further, the computer is essentially a mathematical machine, with the primary capability of rapid and accurate evaluation of numerics. Unfortunately, medical researchers may be relatively unsophisticated in mathematics. However, the boundaries which have separated computer science from medical technology can be broken down through programming and input-output devices so as to provide the medical researcher with a tool with which he can work comfortably and freely. Although the medical researcher cannot be expected to have a high level of knowledge in computer science as well as in his own specialty, he must develop the ability to program his problems in a manner suitable to the computer technology provided by his computer scientist colleagues.<sup>8</sup>

Medicine is now on the threshold of realizing the potential of the computer. The transition of medicine from a descriptive to an analytic science is accelerating; there is more financial support for new equipment, and mathematical and computer science competence is expanding into the biomedical work of physical scientists and engineers. Such specialties as bio-electronics, bio-medical engineering, physical biology, neurochemistry, and bio-mathematics, as well as biochemistry, are breaking down the traditional lines dividing professional specialties. The most pressing task now is the adaptation and expansion of computer technology to fit the changing requirements of medical research.<sup>9</sup>

In this area, a computer which helps clinicians to determine the difference between normal and cancerous cells has been developed at the University of Chicago. Known as TICAS (Taxonomic Intracellular Analytic System), it makes

finite distinctions between cells that otherwise could not be detected. As the microspectrophotometer scans cells, diagnostic information is transmitted automatically to the computer. This system has been programmed with information from expert cytopathologists from all over the world. Remembering every cell it scans, the computer can identify unknown cells to determine if they are cancerous. TICAS will soon be detecting premalignant and early malignant conditions for clinics. In this way it will help to establish reproducible cytopathologic standards, help control the quality of tissue cultures, and assess the threshold effects on cells of drugs, viruses, and radiation.<sup>10</sup>

Consulting the literature instead of the consultants is another job that a well-programmed computer handles with ease. The National Library of Medicine has for some time been using a computer system called MEDLARS (Medical Literature Analysis and Retrieval System) to keep track of hundreds of thousands of medical articles. This system is now cross-indexing some 250,000 articles each year, and, according to Doctor Richard M. Magraw,<sup>11</sup> may someday largely supersede the *Index Medicus*. Since computers can examine data faster and more accurately than men can, the doctor's request for a bibliography on a given subject can be answered promptly by a computer retrieval system, saving hours or even days of search time.<sup>11</sup>

## Diagnosis and Treatment Planning

The necessity for computer aid in medical diagnosis and treatment planning is more apparent each day. Such methods will be required to make multiphasic screening a practical and feasible procedure; even the use of computers in the physician's office by means of telephone or remote console may become a practical necessity in the future. Already, computer methods are being introduced into outpatient clinics to assist with their ever-increasing load. But before such use of computers becomes widespread, many outstanding problems must be solved. First, the process of evaluating the patient's symptoms, whether by clinical examination or by laboratory test, must become more accurate. Much has been written on the subject of diagnostic error, most of which results from errors in symptom evaluation. Second, computer methods, including relevant mathematical analysis,



must be further improved to take into account the practical problems that have been discovered to date. And, finally, the collection of data must be systematically automated so that such things as input numbers, probabilities, and values can be conveniently collected and transmitted to the proper users in the correct form.<sup>12</sup>

When the problems discussed above are solved, the computer will be able to: (1) produce a list of possible diagnoses consistent with the medical knowledge for a given set of symptoms presented by the patient; (2) indicate further diagnostic tests which best differentiate among remaining diagnostic possibilities; (3) calculate the probabilities for alternative diagnostic possibilities; (4) enable a more precise statement and analysis of the value decisions which may be associated with treatment planning; (5) compile statistics which relate symptom-disease combinations and which evaluate disease-treatment prognosis results; (6) make feasible the utilization of more quantitative criteria that has heretofore been possible in the evaluation of the results of certain diagnostic procedures (such as electrocardiograms and electroencephalograms), as well as perform the complicated calculations necessary for the proper interpretation of many other clinical measurements; (7) significantly aid medical-information retrieval (for example, the computer is able to rapidly retrieve current information about new preventive measures, diagnostic techniques, and specific treatments). Finally, the computer is able to: (8) easily accumulate and recall desired aspects of a particular patient's total medical record, such as total radiation dose received, previous allergic reactions, and individual biochemical and physiologic norms and deviations.<sup>13</sup>

The first in a series of automated multiphasic screening and testing systems has been installed in Cherry Hill, New Jersey to perform health appraisals as a service to individual physicians, industries, unions, and government organizations. This system features the use of computer techniques to permit direct interaction of the patient testing station with a high-speed data processor. Patients move through a complete battery of tests and measurements which results in a detailed health profile. No diagnosis is accomplished as a part of the process. Rather, the results of the various tests are printed in a form convenient for physician analysis. A wide battery

of diagnostic tests are provided, including medical history, blood analysis, urinalysis, cytology, anthropometry, spirometry, chest x-ray, visual acuity audio acuity, tonometry, electrocardiogram, blood pressure, and other cardiovascular measurements. In addition, plans are under way to utilize advanced techniques for the early detection of cancer of the breast. This program is the first application of the new Searle Medidata system to large scale health screening by private industry, and is similar to one in operation at the Alta Bates Community Hospital in Berkeley, California.<sup>14</sup>

The model for all other currently functioning multiphasic screening clinics is the one conducted by the Kaiser Foundation Health Plan, Inc., in Oakland and San Francisco, California. On the basis of the experience of the Kaiser-Permanente program, automation of the laboratory aspects of the periodic health examination has proven to be successful. Some of the major advantages in the multitest laboratories are that the patient receives a large battery of tests in an efficient and inexpensive manner, and the physician is supplied with comprehensive, quality information which conserves his time and aids him in the management of the patient. When an average of 500 persons are tested per week, the total per person cost of such testing has been calculated at \$21.32. Of this, the cost of the data processing aspects is \$4.50. In addition to recording results of individual tests, the computer is programmed to call for such additional testing as may be considered medically advisable and to arrange for follow-up appointments with a physician.<sup>15</sup>

### Problems in Computer Application

Aside from the technical problems, such as programming, some of the major barriers encountered in adapting computer usage to the health care field should be discussed. Perhaps the most far-reaching of these problems is the education of the personnel involved. Ease of utilization is of primary importance at every level, from the physician to the nurses' aide; and this necessary familiarity can come only through education in computer usage. Although full discussion of this subject is not within the scope of this *Report*, it should be noted that unless the physician, nurse, or hospital administrator knows how to utilize it properly and fully, the

largest computer in the world would be nothing more than an expensive nuisance.

Thus enters the second barrier to widespread immediate automation: cost. These two factors, cost and education, are inextricably linked in the following fashion: a large proportion of the hospitals in the United States today could afford the services of a computer, at least on a time-sharing basis. (Under the time-sharing system, one or more rented teletypewriters are linked to a central computer, which can handle a large number of incoming calls simultaneously.) However, there is no such thing as half-way automation of, for example, admissions data or medication orders. And the process of training all the physicians who use the hospital, plus three shifts of nurses, bookkeepers, ward secretaries, and all the other personnel involved, in the fundamentally simple (from the user's point of view) techniques of computer usage, is prohibitively costly and time-consuming. Since there is no point, and some definite disadvantages, in installing a system that cannot be used efficiently, there must be a gap of at least one educational generation before computer installation in most hospitals can be considered feasible.

A third problem, noted above, is that the engineer, electronics expert, or computer specialist does not have the same viewpoint about problems of medical care as does the physician. Devices and aids, including some types of computer application such as monitoring devices, that would be ideal in theory, often must be modified drastically to be acceptable in practice to the physician and his patient. More is involved here than the usual difficulties encountered in the practical application of "pure" research, since the researcher is often in another field entirely, with little grasp of the physician's or the patient's needs; hence, the emergence of such specialties as biomedical engineering and electronics.

A fourth, and final problem is that many practicing physicians fear that the intrusion of electronic devices, particularly the use of computers in such areas as screening examinations and diagnostics, will interfere with the traditional doctor-patient relationship. In considering this problem, two points must be kept in mind; the computer is essentially a calculating machine, capable of providing extremely fast comparisons and statistics for huge sets of data and possessed

of an enormous and, for practical purposes, infallible memory; and second, the computer is capable of neither judgment nor decision on its own, and can work only with the methods which have been supplied by the programmer and the data provided by the user.

Thus, the whole system is designed not to supplant the physician or to usurp his right of judgment, but to allow him quick access to the latest medical knowledge and opinion on the subject in which he is interested. Ideally, in fact, the computer will be able to relieve the physician of some of his more mechanical tasks and will provide an efficient means of keeping up to date on the areas of medicine most important to him. Indeed, unless expanding population and acute manpower shortages dictate otherwise, the physician is likely to find that he has more time to devote to his patients as individuals, and to gather more information of the type that cannot be handled by the computer—that part of the diagnosis which is based on subtle and personal cues.

There are many ways in which computers may significantly aid the physician. However, it should not be implied that computers will make the physician's job easier. On the contrary, he must learn to communicate with the computer and how to evaluate correctly the information obtained from it. Once physicians and other medical personnel have done this, however, the increased ability to make a precise diagnosis and to choose the optimum possible treatment plan will more than offset the difficulties involved in such utilization of the computer.

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## Information

# Highlights of Auscultation in Congenital Heart Disease

## Part I

JOSEPH K. PERLOFF, M.D.

*Material Supplied by the American  
Heart Association*

THE HEART SPEAKS in a language of its own; its vocabulary consists essentially of sounds and murmurs. Once the vocabulary is understood, considerable insight can be gained into the anatomic and physiologic condition of the heart and circulation.

*The Mitral Orifice*—The commonest cause of obstruction at the mitral orifice is rheumatic mitral stenosis. The auscultatory hallmarks of this disorder consist of a loud first heart sound, increased intensity of pulmonary valve closure, an opening snap; and a middiastolic murmur followed by presystolic accentuation. The skilled clinician not only understands the mechanisms of these signs but also understands how best to elicit them. A loud first heart sound and an opening snap imply good valve mobility and together are features of tight mitral stenosis. Accordingly, these auscultatory events would not be expected in the presence of immobilizing calcification of the leaflets or considerable mitral incompetence. Similarly, a loud pulmonary closure sound (best judged during inspiratory splitting of the second heart sound) reflects an elevated pressure in the pulmonary trunk. A presystolic murmur implies sinus rhythm and dominant mitral stenosis, so that this murmur van-

ishes with the advent of atrial fibrillation or appreciable mitral incompetence. In the presence of atrial fibrillation, the duration of the middiastolic murmur is an accurate mirror of the degree of stenosis; a middiastolic murmur that continues up to the end of the diastole means that the gradient continues to the end of diastole, implying that stenosis is sufficient to prevent the left atrium from effectively emptying.

It is important to remember that the auscultatory signs of mitral stenosis are best heard over the *left ventricular impulse*. It is mandatory that the bell of the stethoscope be placed *precisely* over this impulse which is most readily located by palpating the region of the apex while the patient partially turns to the left. The physiologic effects of turning serve the additional useful purpose of transiently increasing the intensity of the murmur; coughing has a similar effect. Unless the proper positions and maneuvers are employed, the auscultatory signs of mitral stenosis can be overlooked. *Silent* mitral stenosis is rare but may occur when severe pulmonary hypertension causes such enlargement of the right ventricle that it displaces the left ventricular impulse from the chest wall.

*Mitral incompetence* is accompanied by the prototype of the holosystolic murmur, i.e. a murmur that begins with the first heart sound and goes throughout systole up to the second heart sound. Such murmurs are generally maximal at the cardiac apex, although variations must be understood. The murmur of mitral incompetence is known to radiate to the axilla and back, but it occasionally radiates to the left sternal edge, base, and even into the neck where it may be mistaken for the murmur of aortic stenosis. The murmur of aortic stenosis itself—especially in older patients—may be well-heard if not best heard at the apex and incorrectly ascribed to mitral incompetence; this error can be avoided if it is remembered that the murmur of aortic stenosis—irrespective of its chest wall location—is *midsystolic* and ends before the second heart sound (see below).

There are two important deviations from the classic holosystolic murmur of mitral incompetence. A *late* systolic murmur preceded by one or more systolic clicks may accompany prolapse of a redundant posterior mitral leaflet. Although the degree of mitral incompetence is generally mild in such patients, it is important to recognize the significance of clicks and late systolic murmurs since the deranged mitral valve is susceptible to

This article is to be published in two parts. Part II will appear in a subsequent issue.

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bacterial endocarditis. An *early* systolic or *decrecendo* systolic murmur is a feature of *severe* mitral incompetence of recent onset as with ruptured chordae tendinae; under these circumstances, the major part of regurgitation occurs in early systole since a very high left atrial pressure results in a striking increase in the resistance to left atrial filling in latter systole.

**The Tricuspid Valve**—The murmur of tricuspid stenosis is commonly missed even though this valvular defect occurs in 2 to 3 percent of patients with rheumatic mitral stenosis. Several guidelines set the stage for clinical recognition. The murmur is confined to a localized area along the lower left sternal edge, is presystolic with sinus rhythm and middiastolic with atrial fibrillation. The most distinctive feature is the selective inspiratory increase in loudness; during inspiration the tricuspid gradient increases and with it the intensity of the murmur.

When tricuspid *incompetence* occurs with an *elevated* right ventricular systolic pressure (pulmonary hypertension or congestive heart failure), there is a high velocity of regurgitant flow throughout systole and a relatively high frequency holosystolic murmur that selectively increases during inspiration (Carvallo's sign). Occasionally tricuspid incompetence occurs with *normal* right ventricular systolic pressure as with Ebstein's anomaly or following tricuspid endocarditis caused by "main line" administration of addictive drugs. Under these circumstances, a low velocity of regurgitant flow occurs chiefly in early systole so the murmur is relatively low frequency and early systolic but still selectively increases during inspiration.

**The Aortic Valve**—The aortic stenotic murmur is the model of the midsystolic murmur, *crecendo-decrecendo* in shape, beginning after the first heart sound or with an ejection sound, and

ending before the aortic valve closure. In valvular aortic stenosis the murmur is maximal in the second right intercostal space with radiation upward, to the right, and into the neck. In older patients, especially those with calcific aortic stenosis, the murmur in the second right interspace may be harsh and grunting whereas the murmur at the apex pure and musical. It is important to remember that the classic midsystolic murmur of aortic stenosis is sometimes absent altogether in patients with severe obstruction; left ventricular failure may result in a substantial decrease in flow across the stenotic valve with disappearance of the midsystolic murmur or replacement by the holosystolic murmur of mitral incompetence. In the presence of an increase in antero-posterior chest dimensions (emphysema) the basal murmur may soften or vanish although radiation into the neck persists.

The typical murmur of aortic *incompetence* is readily recognized especially when loud and accompanied by bounding arterial pulses. However, faint high frequency murmurs of mild aortic incompetence are difficult to hear and must be specifically sought by applying very firm pressure of the stethoscopic diaphragm to the mid-left sternal border while the patient sits or stands, leans forward, and holds the breath in full expiration. Squatting—by raising aortic root pressure—tends to augment these faint murmurs and serves a useful purpose in their detection which is important because of susceptibility to endocarditis. The direction of the blowing early diastolic murmur should be determined by comparing its loudness along the left and right sternal borders especially at the third intercostal spaces. Prominent radiation to the right sternal border suggests a non-rheumatic etiology such as aortic root disease or specific cusp deformity.

*(Continued in Part II to be published in a subsequent issue.)*



# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## The Physician's Role in Venereal Disease Control

VENEREAL DISEASE (VD) is a serious public health and community problem in California. In 1970, it was the leading notifiable communicable disease for the ninth consecutive year with 103,000 reported gonorrhea cases and 11,000 reported syphilis cases. Case rates for gonorrhea rose from 121.3 per 100,000 in 1960 to 516.2 in 1970, more than a fourfold increase. California with 10 percent of the nation's population has 16 percent of its reported VD cases. Young people under 25 have over half of all cases.

To help to solve this critical problem, the State Board of Public Health established the California Venereal Disease Control Task Force, composed of representatives of broad segments of the community. The Task Force is charged with reviewing the extent and nature of the problem in California and making recommendations for corrective action to the State Board of Health, the California Medical Association, the State Department of Education and the State Board of Pharmacy.

Physicians, who in the campaign to control VD, see the majority of cases, play a significant role. It is important to maintain a high index of suspicion about VD and report all cases to local health departments. Early reporting makes it possible to reach the infected person's contacts promptly for the epidemiologic treatment so indispensable to VD control. When a physician diagnoses a case

of infectious syphilis, he should report it by telephone and follow it up with a written report.

In addition to physical examination and laboratory studies of gonorrhea contacts and primary and secondary syphilis contacts, physicians should provide prompt epidemiologic treatment to such contacts, without waiting for laboratory results or relying upon obvious lesions or discharges as evidence of VD.

The following products and dosages are currently successful therapy for gonorrhea (uncomplicated male urethritis) in California venereal disease clinics:

### *Injection*

1. Aqueous procaine penicillin, 2.4 million units. (May repeat next day; especially for women and rectal disease.)
2. Aqueous procaine penicillin, 2.4 million units, with probenecid 5 grams. (Probenecid, 1 gram half hour before injection, then 1 gram q.i.d.)
3. Cephaloridine, 2 grams. (May repeat next day.)
4. Tetracycline, 250 mg. (May repeat next day.)
5. Streptomycin, 2 grams (with sulfonamides, 20 grams divided over 5 days.)

### *Oral*

1. Ampicillin, 3 grams. Given over 3 days: One gram stat.; then 0.5 gram at 4 and 8 hours, then 0.5 gram b.i.d. (Females given 0.5 gram b.i.d. one additional day—total, 4 grams.)
2. Demethylchlortetracycline (Declomycin®), 2700 mg. Given over 4 days: 600 mg stat., 300 mg at 8 hours, then 300 mg b.i.d. x 3.
3. Doxycycline (Vibramycin®), 800 mg (200 mg stat., 100 mg b.i.d. x 3). (Females given 100 mg b.i.d. for two additional days—total, 1200 mg.)

4. Tetracycline, 10 grams (1.5 gram stat.; then 0.5 gram q.i.d. x 4).

VD can be expected to develop in 20 to 50 percent of named sexual contacts. Treatment of syphilis or gonorrhea contacts at the time of initial examination can destroy infecting organisms in the incubation period.

Symptoms of gonorrheal infection in the female genito-urinary tract or rectum may be minimal or even absent in 80 percent of cases. Easily missed, too, are symptoms of early syphilis. Serologic tests do not become positive until late in the primary stage, by which time the disease is highly communicable. Since the infectious period of syphilis can be long, recent contacts need observation and repeated examinations for at least three months after exposure. Often the patient does not return for the necessary subsequent examinations. Such delays in making a diagnosis of VD allow the development of serious complications among those infected and permit the further spread of infection in the community.

Homosexuality is also implicated in the spread of VD, its frequency being higher in patients with infectious syphilis than in those with gonorrhea. Routine physical examination of patients and contacts should include all significant body orifices, visible mucous membranes and mucocutaneous junctions.

Until vaccines against syphilis and gonorrhea are developed, prophylaxis and education provide the best hope for control. Experience in World Wars I and II demonstrated that condoms, properly used, help prevent the spread of VD. Some public health personnel have urged that sexually

active persons consistently use condoms, and their use is gaining acceptance. Physicians may wish to recommend them and might also consider suggesting to women that they insist that their partners use them. Physicians, public health officers and pharmacists may now legally give advice for prevention of VD, even to minors.

Hygienic measures immediately before and after sexual activity also reduce infection. Soap and water effectively reduce bacteria. After intercourse females should douch with a hygienic solution. Urination after intercourse provides some protection against gonorrhea, particularly in males.

Several courses of action are open to physicians who wish to engage in VD education in the community. The California Congress of Parents and Teachers as well as the National Congress of Parents and Teachers endorse and encourage VD education in the public schools. Physicians are in a unique position to assist them in this endeavor. Physicians are also encouraged to discuss VD in medical association and hospital staff meetings. Local health departments and the State Department of Public Health will arrange to provide speakers from their own staff or from medical, voluntary or civic organizations in local communities.

Two excellent articles on several aspects of VD are recommended: Walter H. Smartt, M.D., and Andrew G. Lighter, M.D., "The Gonorrhea Epidemic and Its Control," and Warren A. Ketterer, M.D., "Homosexuality and Venereal Disease," in *Medical Aspects of Human Sexuality*, Vol. V, Nos. 1 and 3, respectively, 1971.



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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AMIR, MICHAEL M., Hawthorne. Died February 27, 1971 in Playa Del Rey, aged 42. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1959. Licensed in California in 1960. M.D. degree from California College of Medicine, 1962. Doctor Amir was a member of the Forty First Medical Society.

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ANDERSON, BENJAMIN NELSON, Burbank. Died March 21, 1971 in Sepulveda of pyelonephritis, aged 65. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Anderson was a member of the Los Angeles County Medical Association.

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BAETZ, WALTER GUSTAVE, Huntington Park. Died March 23, 1971 in Los Angeles of cardiovascular accident, aged 86. Graduate of Eclectic Medical College of the City of New York, 1906. Licensed in California in 1919. Doctor Baetz was a member of the Los Angeles County Medical Association.

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BLANFORD, TOBY MADISON, Pomona. Died February 28, 1971 near Gallup, New Mexico, in an automobile accident, aged 35. Graduate of University of Iowa College of Medicine, Iowa City, 1964. Licensed in California in 1965. Doctor Blanford was a member of the Los Angeles County Medical Association.

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CALKINS, ROBERT SARGENT, Riverside. Died February 25, 1971 in Riverside of leukemia, aged 50. Graduate of University of Oklahoma School of Medicine, Oklahoma City, 1947. Licensed in California in 1955. Doctor Calkins was a member of the Riverside County Medical Association.

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CHAMOVE, ARNOLD SAMUEL, San Francisco. Died March 1, 1971 in San Francisco, aged 68. Graduate of University of Oregon Medical School, Portland, 1928. Licensed in California in 1938. Doctor Chamove was a member of the San Francisco Medical Society.

DAUS, ERNEST A., Alameda. Died February 27, 1971 in Santa Clara, aged 79. Graduate of University of Oregon Medical School, Portland, 1917. Licensed in California in 1944. Doctor Daus was a retired member of the Solano County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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DUNCKEL, WILLIAM C., JR., San Jose. Died February 8, 1971 in San Jose, aged 49. Graduate of Washington University School of Medicine, St. Louis, 1947. Licensed in California in 1960. Doctor Dunkel was a member of the Santa Clara County Medical Society.

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ESHMAN, LOUIS AARON, Los Angeles. Died March 2, 1971 in Los Angeles of cardiovascular disease, aged 69. Graduate of University of Illinois College of Medicine, Chicago, 1925. Licensed in California in 1926. Doctor Eshman was a member of the Los Angeles County Medical Association.

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FELGER, LOUIE, Beverly Hills. Died February 24, 1971 in Los Angeles of myocardial infarction, aged 78. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1914. Licensed in California in 1914. Doctor Felger was a member of the Los Angeles County Medical Association.

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GRAU, EUGENE CLAIR, Fremont. Died March 1, 1971 in Fremont of anoxia due to bronchopneumonia, aged 70. Graduate of University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1926. Doctor Grau was a member of the Alameda-Contra Costa Medical Association.

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HANSEN, FREDERIK L., Berkeley. Died March 16, 1971 near Salinas in a plane crash, aged 42. Graduate of University of Texas Medical Branch, Galveston, 1956. Licensed in California in 1965. Doctor Hansen was a member of the Alameda-Contra Costa Medical Association.

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HEMPHILL, WAYNE A., Victorville. Died February 16, 1971 in Loma Linda, aged 41. Graduate of the University of Texas Southwestern Medical School, Dallas, 1960. Licensed in California in 1961. Doctor Hemphill was a member of the San Bernardino County Medical Society.

KATZ, LEONARD, Canoga Park. Died February 2, 1971 in Los Angeles of heart disease, aged 42. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1959. Licensed in California in 1959. M.D. degree from California College of Medicine, 1962. Doctor Katz was a member of the Los Angeles County Medical Association.

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LANGAN, ARTHUR J., San Pedro. Died February 17, 1971 in San Pedro, aged 81. Graduate of the University of Illinois College of Medicine, Chicago, 1914. Licensed in California in 1918. Doctor Langan was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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LECKIE, FRANK PENTLAND, Santa Barbara. Died February 25, 1971 in Santa Barbara, aged 52. Graduate of McGill University Faculty of Medicine, Montreal, 1943. Licensed in California in 1951. Doctor Leckie was an associate member of the Santa Barbara County Medical Society.

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MILLER, PALMER DONALD, Fresno. Died March 15, 1971 in Fresno of carcinoma, aged 65. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Miller was a member of the Fresno County Medical Society.

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NIJASI, ALI RACHIMOGLI, Olive View. Died February 6, 1971 in San Fernando of carcinoma, aged 48. Graduate of Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, Prussia. Licensed in California in 1964. Doctor Nijasi was an associate member of the Los Angeles County Medical Association.

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RIDDELL, ORIN JOSEPH, Hillsboro, New Mexico. Died September 8, 1970 in Hillsboro of heart disease, aged 72. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1926. Doctor Riddell was a member of the Los Angeles County Medical Association.

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RUCH, MONROE KUNTZ, Monterey Park. Died February 21, 1971 in La Paz, Mexico, of emphysema, aged 60. Graduate of University of Chicago, The School of Medicine, 1936. Licensed in California in 1936. Doctor Ruch was a member of the Los Angeles County Medical Association.

SALBERG, ARTHUR KELLER, Los Angeles. Died March 1, 1971 in Los Angeles of chronic obstruction-pulmonary disease, aged 58. Graduate of University of Illinois College of Medicine, Chicago, 1940. Licensed in California in 1948. Doctor Salberg was a member of the Los Angeles County Medical Association.

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SHELTON, ROBERT MCNEIL, Pasadena. Died March 13, 1971 in Pasadena of coronary artery disease, aged 58. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1937. Doctor Shelton was a member of the Los Angeles County Medical Association.

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SHERMAN, GEORGE FAIRCHILD, San Francisco. Died March 21, 1971 in San Francisco of heart disease, aged 59. Graduate of University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Doctor Sherman was a member of the San Francisco Medical Society.

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SKAGGS, MARSHALL L., Sacramento. Died March 10, 1971 in Sacramento, aged 63. Graduate of University of Cincinnati College of Medicine, 1941. Licensed in California in 1946. Doctor Skaggs was a member of the Sacramento County Medical Society.

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SMITH, WALLACE BRUCE, San Francisco. Died March 2, 1971 in San Francisco of heart disease, aged 91. Graduate of Birmingham Medical College, Alabama, 1903. Licensed in California in 1906. Doctor Smith was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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SMITH-SWIFT, GLADYS GRACE, Newport Beach. Died February 8, 1971 in Newport Beach of myocardial infarction, aged 60. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1941. Licensed in California in 1943. Doctor Smith-Swift was a member of the Los Angeles County Medical Association.

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THAYER, JANET CAMPBELL, Canoga Park. Died February 20, 1971 in Los Angeles of carcinoma, aged 66. Graduate of University of Illinois College of Medicine, Chicago, 1932. Licensed in California in 1942. Doctor Thayer was a member of the Los Angeles County Medical Association.

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WHARTON, GEORGE K., Los Angeles. Died February 14, 1971 in Los Angeles of myocardial infarction, aged 66. Graduate of University of Toronto Faculty of Medicine, 1927. Licensed in California in 1946. Doctor Wharton was an associate member of the Los Angeles County Medical Association.



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# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**PATHOLOGY ANNUAL 1970**—Volume Five—Series Editor, Sheldon C. Sommers, M.D., Director of Laboratories, Lenox Hill Hospital, New York, N.Y.; Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons, New York; Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles. Appleton-Century-Crofts, Educational Division, Meredith Corporation, 440 Park Avenue South, New York, N.Y. (10016), 1970. 436 pages, \$15.00.

This *Pathology Annual*, edited by Sheldon C. Sommers, is the fifth in a series of excellent essays and reviews by distinguished pathologists. Like previous *Annals*, it contains a wide range of currently interesting and important subjects.

Fisher and Sieracki concisely describe the ultrastructure of human normal and neoplastic prostate, but conclude that the advantages of EM evaluation of prostatic tissue are limited at present. Embryonal carcinoma of the testis is discussed by Pierce and Abell, particularly the histogenesis and pathology of these germ-cell neoplasms. Higginson and Svoboda review current information on primary carcinoma of the liver, including geographic pathology, experimental liver cancer, relationship to cirrhosis, and a listing of possible hepatocarcinogens. Some recent studies, however, link more intimately the persistence of the Australian antigen in hepatocellular carcinoma than do these authors. Diagnostic problems involving nodal lymphomas are reviewed by Sieracki and Fisher, who contrast malignant lymphomas with a number of non-lymphoma lymph node lesions to illustrate the pitfalls contributing to diagnostic failure. McCluskey details the structural features of lupus nephritis as visualized by light and electron microscopy and immunofluorescence and neatly reviews present concepts of its pathogenesis.

The biochemical and ultrastructural characteristics of adrenal medullary tumors are correlated by Tannenbaum, who suggests that further study of such neoplasms would be clinically useful for more accurate prognosis and therapy. Fetterman beautifully reviews renal structure and function studied by microdissection of nephrons and collecting ducts, and emphasizes the value of this morphologic technique. A fascinating story of Kaiser Frederick III and his affliction (carcinoma of the larynx) is recounted by Ober. Ioachim extensively reviews the tissue culture of human neoplasms and briefly discusses the use of this technique for screening and testing chemotherapeutic agents. A considerably informative organizational plan for hospital tumor registries is outlined by Olson, Stone and Harlan, who stress the usefulness of data thus accumulated. A contemporary view of lung injury and repair is offered by Bowden and Wyatt, demonstrating a unifying concept of the limited lung pathways of reaction to injury. Dutz contributes a very complete and well illustrated pathologic and clinical review of pneumocystis carinii pneumonia. The ultrastructural aspects of acute inflammation, with particular reference to vascular permeability and leukocyte emigration, are discussed by Marchesi. Dixon and Cochrane thoroughly describe and illustrate the pathogenic effects of antigen-antibody complexes, both in experimental and in human lesions.

A most instructive treatise on the use of polarized light in pathology, including the application of such microscopy to biology, is presented by Wolman.

The concluding chapter of the *Annual* comprises another of Foraker's delightful plays, depicting in seven scenes a day in the lives of some academic pathologists.

This 1970 *Annual* should be of great interest to many clinicians as well as to pathologists in general.

STUART LINDSAY, M.D.

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**CURRENT PSYCHIATRIC THERAPIES**—Volume X—1970—Edited by Jules H. Masserman, M.D., Professor of Psychiatry and Neurology, Northwestern University, Chicago. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 239 pages, \$14.75.

This volume maintains the same high level of quality and progressive interest in new developments in the field that past volumes have done. Its strengths greatly outnumber its weaknesses. The same comments this reviewer made on last year's volume still apply, and will be repeated here.

Both the selection of articles and the quality of writing is good. Each of the articles represents a new, imaginative, sometimes-controversial-but-certainly-worth-trying approach to a psychiatric problem. Some of the techniques described here in pilot form will grow and become accepted parts of psychiatric practice in future years; others will fade into oblivion. My crystal ball is off to my astrologers' to have its vibrations tuned, so I won't hazard a guess as to which of the articles in *Current Psychiatric Therapies* of 1970 are truly harbingers of things to come.

I was impressed by the clarity, brevity and crispness of the writing. The book is easy to read. Credit for this must go to the editor, Jules Masserman, whose eye or hand (or both) insured the book's readability. I commend the book to psychiatrists and non-psychiatrists alike who are curious about new directions in the field and who would like to know about interesting pilot projects already in operation.

The price of \$14.75 seems high.

C. PETER ROSENBAUM, M.D.

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**THE EARLY ORTHOPAEDIC SURGEONS OF AMERICA**—Alfred Rives Shands, Jr., M.D., Medical Director Emeritus, Alfred I. duPont Institute of the Nemours Foundation, Wilmington, Delaware; President of the American Orthopaedic Association, 1953-1954; Historian of the American Orthopaedic Association, 1965-1970; Visiting Professor of Orthopaedic Surgery, University of Pennsylvania School of Medicine, 1941-1970; Associate Professor of Surgery in Charge of Orthopaedics, Duke University School of Medicine, 1930-1937. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1970. 190 pages, with 156 illustrations, \$15.00.

The growth of orthopedic surgery in the United States since World War II can only be designated by the word 'fantastic'. But this growth arose from vital and deeply established roots which nourished the formation of its branching second phase which occurred between the



wars to create the present efflorescence. The author, Dr. Shands, is a distinguished leader in the development of the more scientific second phase of orthopedics and therefore an ideal interpreter of the transition from the period of the "strap and buckle" pioneers to the present, maintaining that essential historical continuity expressed in his own quotation: "The heritage of the past is the seed that brings forth the harvest of the future."

In twelve carefully documented biographies Dr. Shands presents to us the work of the early orthopedic surgeons of America. What a galaxy of ingenious and dedicated men they were, whose names are household words in medicine although unfortunately their personalities and the nature of the contributions are not. William Dismold, first American orthopedic surgeon; Louis Bauer, author of the first American orthopedic textbook; Lewis Sayre, first professor of orthopedic surgery; Henry Davis, founder of the American school of orthopedic surgery; James Knight, founder of the Hospital for the Ruptured and Crippled; Virgil Gibney, teacher of master surgeons; Charles Taylor of the Taylor brace; Newton Shaffer, conservative organizer of the specialty; John and Buckminster Brown, father and son of the Boston school; Edward Bradford, of the Bradford frame; DeForest Willard, rehabilitator of the crippled child.

Interestingly written and well illustrated, this attractive work should be in the hands of all orthopedic surgeons and especially those in residency training. The medical historian welcomes a work which enriches his view of the growth and development of American medicine.

J. B. DEC. M. SAUNDERS, M.D.

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**THE TRUTH ABOUT CONTACT LENSES**—Everything the Wearer, or Potential Wearer, Should Know—Jeffrey Baker. G. P. Putnam's Sons, 200 Madison Avenue, New York, N.Y. (10016), 1970. 248 pages, \$5.95.

This is a remarkably comprehensive and informative discussion of the pros and cons of contact glasses. Written by a layman for laymen it is recommended for study by all those persons having to do with the prescribing, fitting, manufacture and wearing of these lenses as well.

Mr. Baker, a contact glass wearer, was unable to find answers to many questions regarding these lenses and their advantages and disadvantages. He has thoroughly researched his subject and this book is the result.

The book is a fair and unbiased appraisal of the whole subject of contact glasses. It points out in considerable detail why some persons do well with the lenses almost from the start while others find them intolerable. The advantages of contact lenses are documented and, with equal fairness, their disadvantages and dangers are described. Various myths about contact glasses are exploded. The methods of fitting the lenses are described and compared with the prescribing of spectacles. The chapters on adapting to contact glasses and on the troubles which may beset the adapted or even the veteran wearer are especially valuable. Finally, an entire chapter devoted to practical tips for lens wearing success is worth the price of the entire book.

The layman should find the chapters on eye anatomy, the nature of contact lenses and the history of their development, and the manner in which they effect visual improvement of considerable interest.

Those practitioners who have anything to do with the fitting of these lenses, whether they be ophthalmologists, optometrists, or technicians working with opticians under the direction of ophthalmologists should be especially interested in the portions of this book describing the dan-

gers of improperly fitted lenses, overwearing of lenses, dependence on contact glasses and the possibilities of permanent damage to the eye from these devices. I heartily recommend this book to all such practitioners.

DAVID O. HARRINGTON, M.D.

• • •

**A BIOGRAPHICAL HISTORY OF MEDICINE**—Excerpts and Essays on the Men and Their Work—John H. Talbott, M.D., Formerly Professor of Medicine, University of Buffalo School of Medicine, Physician-in-Chief, Buffalo General Hospital, and Editor, Journal of the American Medical Association and Director of the Division of Scientific Publications. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 1211 pages, \$60.00.

The biographical précis is a thankless task of scientific writing. Dr. Talbott, while editing the JAMA and putting color on its covers, spent many evenings and weekends composing these essays, which were published in the JAMA. Many, because of letters to the editor, were revised and expanded. The biographies begin with Hammurabi and end with Banting. Only one physician living at the time of printing is included. The nearly 500 mini-biographies include the salient details, but occasionally leave out spicy items of the subject. For example, Talbott does not tell why Moritz Kohn changed his name to Kaposi. All in all, the panorama of medicine is spanned biographically. Of greatest value in the book's contents are the extracts from the publications of the biographies. Here, conveniently in one volume, the reader can find the original statement of the great verities of medicine.

This book is tasty bait for the reviewer's malady—carping about minutiae and crabbing about omissions. It is possible that obstetricians may groan because the Chamberlens of forceps-fame are missing, and psychiatrists may object to the absence of Henry Stack Sullivan and Carl Jung. Cardiologists may ponder why Marey and Paul Wood are missing, and internists may look in vain for George Dock and the Peppers of Philadelphia. Surgeons may wonder that Souttar, Homans, and O'Shaughnessy are not included. And if Somerset Maugham is given a place because of Talbott's broad interest, what of Wilfred Trotter and Parkes Weber? Historians will be annoyed by the omission of Fielding Garrison, whose history of medicine Talbott no doubt consulted hundreds of times while composing the biographies.

This interesting book is aimed at medical students and those practitioners whose interests include the history of our noble art. No other single volume even approaches it in completeness. For libraries it is a must. The price of \$60 will regrettably keep it from the shelves of many whose leisure would be made more enjoyable by it.

EDWARD SHAPIRO, M.D.

• • •

**THE HISTOGENESIS OF THYROID CANCER**—N. Simionescu, Institute of Endocrinology, Department of Morphology, Bucharest, Romania. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 173 pages, \$22.75.

This monograph, based on a study of 368 patients in Bucharest, deals with the pathology and clinicopathologic course of thyroid cancer. In reality, it is a potpourri of information that is extremely difficult to read and digest. The author's classification of thyroid cancer is unique and not readily related to pathologic classifications currently accepted in the United States, Europe, and elsewhere. Most of the photographs are technically acceptable, but many lack structures that are indicated by the accompanying legends. This monograph cannot be recommended for students of thyroid disease.

STUART LINDSAY, M.D.

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# BOOKS RECEIVED

*Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

**BECKER-SHAFFER'S DIAGNOSIS AND THERAPY OF THE GLAUCOMAS—Third Edition**—Allan E. Kolker, M.D., Associate Professor of Ophthalmology and Associate Director of the Glaucoma Center, Department of Ophthalmology, Washington University School of Medicine, St. Louis; and John Hetherington, Jr., M.D., Assistant Clinical Professor of Ophthalmology and Associate Director of the Glaucoma Center, University of California Medical Center, San Francisco. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1970. 495 pages, with 383 illustrations and 6 color plates, \$25.00.

**CLINICAL OBSTETRICS AND GYNECOLOGY—Volume Thirteen, Number Three—Fetal Physiology**, Edited by Leon I. Mann, M.D.; and Psychosocial Problems in Obstetrics and Gynecology, Edited by Mary Anna Friederich, M.D. Harper & Row, Publishers, Inc., 49 East 33rd Street, New York, N.Y. (10016), 1970. Published Quarterly, by Subscription Only, \$22.00 per year.

**EMERGENCY CARE AND TRANSPORTATION OF THE SICK AND INJURED**—The Committee on Injuries, American Academy of Orthopaedic Surgeons. American Academy of Orthopaedic Surgeons, 430 North Michigan Avenue, Chicago, Ill. (60611), 1971. 294 pages, no price listed.

**A FILMSTRIP PRESENTATION—Hematology: A Morphologic Study**—Bong Hak Hyun, M.D., D.Sc., Director of Laboratories, Muhlenberg Hospital, Plainfield, N.J.; Clinical Associate Professor of Pathology, Rutgers Medical School, New Brunswick; Visiting Professor of Pathology, Yonsei University College of Medicine, Seoul; Minerva Blank, Ph.D., Supervisor, Hematology Laboratory, Muhlenberg Hospital, Plainfield; and R. Philip Custer, M.D., Professor of Pathology, University of Pennsylvania School of Medicine; Senior Member, The Institute for Cancer Research, Philadelphia. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 84 pages (booklet), 3 filmstrips, \$28.50.

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**NEUTRALITY CONTROL IN THE LIVING ORGANISM—A Learning Program for Students of the Biological and Medical Sciences**—Halvor N. Christensen, Ph.D., Professor of Biological Chemistry and Chairman of the Department, The University of Michigan. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 160 pages, \$5.95.

**PROGRESS IN NEUROLOGY AND PSYCHIATRY—Volume XXV**—Edited by E. A. Spiegel, M.D., Dr. Med. (Hon.), Emeritus Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. Grune and Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 495 pages, \$28.75.

**THE ANATOMY OF AGING IN MAN AND ANIMALS**—Warren Andrew, Ph.D., M.D., Chairman, Department of Anatomy, Indiana University Medical Center. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1971. 259 pages, \$15.00.

**ANESTHESIA FOR THE AGED**—Paul H. Lorhan, M.D., Professor of Anesthesiology, University of California Medical Center, Los Angeles; Chief of the Department of Anesthesiology, Harbor General Hospital, Torrance, California; with a Foreword by William P. Longmire, Jr., M.D., Professor and Chairman, Department of Surgery, UCLA School of Medicine, Los Angeles. Charles C. Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1971. 153 pages, \$8.25.

**BEHAVIORAL SCIENCES AND MENTAL HEALTH: An Anthology of Program Reports (Public Health Service Publication No. 2064)**—Eli A. Rubinstein and George V. Coelho, Editors. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Institute of Mental Health, Chevy Chase, Maryland (20015), 1970. 419 pages, \$2.00. (For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.)

**EVERYMAN'S GUIDE TO ECOLOGICAL LIVING**—Greg M. Cailliet, Paulette Y. Setzer, and Milton S. Love. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1971. 119 pages, \$0.95.

**A GUIDE TO DRUGS IN CURRENT USE**—Edited by J. R. Trousseau, Professor, Clinical Pharmacology, Guy's Hospital Medical School, London. G. P. Putnam's Sons, 200 Madison Avenue, New York, N.Y. (10016), 1971. 207 pages, \$7.95.

**HUMANISTIC PSYCHOLOGY—A Christian Interpretation**—John A. Hammes, Professor of Psychology, The University of Georgia. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1971. 203 pages, \$7.95.

**MIGRAINE—Evolution of a Common Disorder**—Oliver W. Sacks, B.M., B.Ch., Instructor in Neurology, Albert Einstein College of Medicine, New York, Consultant Neurologist, Beth Abraham Hospital; with a Foreword by William Gooddy, M.D., F.R.C.P., Physician, University College Hospital, London and the National Hospital for Nervous Diseases, Queen Square, London. University of California Press, 2223 Fulton Street, Berkeley, Ca. (94720), 1971. 298 pages, \$8.50.

**MENISCUS LESIONS—Practical Problems of Clinical Diagnosis, Arthrography and Therapy**—Prof. Dr. P. Ricklin, Männedorf-Zurich, Priv.-Doz. Dr. A. Rüttmann, Zurich, and Priv.-Doz. Dr. M. S. Del Buono; American Translation by Karl H. Mueller, M.D., Milwaukee. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1971. 142 pages, with 219 illustrations, \$16.75.

**PULMONARY FUNCTION TESTING IN CHILDREN—Techniques and Standards**—George Polgar, M.D., Associate Professor in Pediatrics and Physiology, School of Medicine, University of Pennsylvania; and Varuni Promadhat, M.D., Research Fellow, Children's Hospital of Philadelphia. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 273 pages, \$23.25.

**SHOCK—A Physiologic Basis for Treatment**—Alan P. Thal, M.D., Ph.D., Professor of Surgery, University of Kansas Medical Center; E. B. Brown, Jr., Ph.D., Professor and Chairman, Department of Physiology; Arlo S. Hermreck, M.D., Resident Surgeon, USPHS Post-doctoral Fellow in Physiology; and Hugh H. Bell, M.D., Assistant Professor of Medicine, Section of Cardiology; with a Foreword by Owen H. Wangensteen, M.D., Ph.D., Regents' Professor of Surgery and Chairman Emeritus, University of Minnesota. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. (60601), 1971. 304 pages, \$14.50.

**SIXTH SYMPOSIUM ON ADVANCED MEDICINE—Proceedings of a Conference held at the Royal College of Physicians of London, 23rd February-27th February, 1970**—Edited by J. D. H. Slater, M.A., F.R.C.P. The Williams and Wilkins Company, Baltimore, Maryland (21202), exclusive U.S. agents, 1970. 320 pages, \$11.00.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

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## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. It is funded through a Health Services and Mental Health Administration grant to the California Committee on Regional Medical Programs; Grant No. 3 S02 RM-00019 01S1. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, ext. 241.

## ADOLESCENT MEDICINE

October 16—Childhood and Adolescence. Napa State Hospital, Imola. Saturday. \$15. 8 hrs. Contact: Magno J. Ortega, M.D., Chief of Professional Education, Napa State Hospital, Box A, Imola 94558. (707) 226-2011, ext. 661.

## ALCOHOLISM AND DRUG USE

June 19-20—National Heroin Symposium. Haight-Ashbury Free Medical Clinic, The Psychopharmacology Study Group, UCSF and The Student Association for the Study of Hallucinogens at Medical Science Auditorium, UCSF. Saturday-Sunday. \$30. Contact: David E. Smith, M.D., Department of Pharmacology, UCSF. (415) 666-9000.

June 28-July 2—Community Mental Health Approaches to the Problem of Drugs. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

July 12-16—Community Mental Health Approaches to the Problem of Alcoholism. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

## CANCER

June 19-20—Second Annual Physicians Symposium—The Cancer Viewpoint. American Cancer Society, Contra Costa County Unit at Concord Inn, Concord. Saturday-Sunday. Carcinoma of the breast, gynecological carcinoma, gastrointestinal carcinoma, malignant melanoma, pediatric malignancies, lymphomas. Contact: American Cancer Society, Contra Costa County Unit, 2180 N. California St., Walnut Creek 94596. (415) 934-7640.

September 30-December 9—Current Concepts of Medical Oncology. UCLA. Thursdays weekly.

October 30—Cancer Symposium. Kaiser Foundation Hospital, Sacramento. Saturday. Contact: Bette Shephard, Continuing Education, Kaiser Foundation Hospital, 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

Continuously—Tumor Board—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 2-3 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: Malin Dollinger, M.D., Chairman, Tumor Board, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA: California Medical Association  
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- LLU: Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
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Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 931-8000.
- STAN: Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD: University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.
- UCI: University of California — California College of Medicine, Irvine  
Contact: Donald W. Shafer, M.D., Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine — California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA: University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-7241.
- UCSD: University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF: University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, School of Medicine, University of California, San Francisco 94122. (415) 666-1692.
- USC: University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



## MEDICINE

- June 16-19—**Third Annual Cerebral Function Symposium.** Annual Cerebral Function Symposium at Hotel del Coronado, Coronado. Wednesday-Saturday. Hemispherectomy and Cerebral Function. \$50. 18 hrs. Contact: W. Lynn Smith, Ph.D., Suite 1120, Franklin Medical Center, 2045 Franklin, Denver 80205. (303) 534-0903.
- June 18-19—**Selected Subjects in Electrocardiography.** UCSF and Mt. Zion Hospital and Medical Center at Hilton Hotel, San Francisco. Friday-Saturday. Arrhythmias, conduction disturbances, other selected topics in electrocardiography. \$100. 12 hrs.
- June 22-23—**American Diabetes Association.** Sheraton-Palace Hotel, San Francisco. Tuesday-Wednesday. Contact: H. Richard Connelley, Exec. Dir., 18 E. 48th St., New York 10017. (212) 752-8550.
- June 24-26—**Endocrine Society.** Hilton Hotel, San Francisco. Thursday-Saturday. Contact: Mrs. Nona Lee Mattox, Exec. Sec., ES, 1211 N. Shartel, Oklahoma City 73103. (405) 232-8747.
- July 5-16—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitoring and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P.H., Admin. Assoc., CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- July 7-10—**International Symposium on Psoriasis.** STAN. Wednesday-Saturday.
- July 9-10—**Pulmonary Disease Seminar.** University of California Extension, Riverside at Sproul Hall, University of California, Riverside. Friday-Saturday. \$26. Anatomy and physiology of respiratory tract; pulmonary function testing; epidemiology of respiratory diseases; air pollution and respiratory disease; pulmonary manifestations of systemic disease; tumors; infectious, allergic and obstructive lung disease. \$26. 10 hrs. Contact: Ray Olitt, Program Coordinator, UC Extension, Riverside 92502. (714) 787-4105.
- July 24—**Pathogenesis and Management of Fluid and Electrolyte Imbalance.** PMC. Saturday. Second in a series of four workshops. \$50.
- August 18-22—**Fourteenth Annual Advanced Seminars in Internal Medicine.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday. 24 hrs.
- August 30-September 2—**Epidermal Wound Healing.** UCSF at Del Monte Lodge, Pebble Beach. Monday-Thursday. Cellular Facets of Wound Repair, Cell Kinetics, Quantitation of Repair, Dermal-Epidermal Interactions, Physical and Chemical Factors Affecting Repair.
- September 8—**Sixth Annual Meeting on Kidney Disease.** STAN. Wednesday.
- September 8-12—**1971 Advanced Seminars in Dermatology.** UCI at Newporter Inn, Newport Beach. Wednesday-Sunday. Microbiology of the Skin, Carcinogenesis and Cutaneous Cancer. \$100. 40 hrs. Contact: James Graham, M.D., Dept. of Medicine, UCI. (714) 633-9393, ext. 172.
- September 13-October 1—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three-week course designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid base metabolism, emphasis on practical techniques. \$250. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.
- September 16—**Differential Diagnosis in Internal Medicine.** USC. One Thursday monthly through December 16.
- September 19—**Fifteenth Annual Physicians Symposium on Cardiovascular Disease.** Santa Barbara and Ventura Counties Heart Associations at Biltmore Hotel, Santa Barbara. Sunday. \$20. 7 hrs. Contact: Mrs. Sara Clyde, Exec. Dir., SBCHA, 18 La Arcadia Ct., Santa Barbara 93103. (805) 963-1541.
- September 22—**Eleventh Annual Medical Symposium on Kidney Disease.** Kidney Foundation of Southern California at Ambassador Hotel, Los Angeles. Wednesday. \$25. 8 hrs. Contact: Leonard Gottlieb, Exec. Dir., KFSC, 5880 San Vicente Blvd., Los Angeles 90019. (213) 936-5229.
- September 24—**Multiple Sclerosis.** UCSF. Friday.
- October 8-11—**California Society of Internal Medicine—Annual Meeting.** Newporter Inn, Newport Beach. Friday-Monday. Contact: Cynthia Bell, Exec. Sec., CSIM, 703 Market St., San Francisco 94103. (415) 362-1548.
- October 9-10—**Western Dialysis and Transplant Society.** Hilton Hotel, San Francisco. Saturday-Sunday. Hemodialysis and renal transplantation, research. \$10. 16 hrs. Contact: John R. DePalma, M.D., Olive View Medical Center, 14445 Olive View, Sylmar 91342. (213) 367-2231, ext. 2666.
- October 14-15—**Diabetes.** USC. Thursday-Friday.
- October 14-16—**Forty-First Annual Physicians Symposium on Heart Disease.** San Francisco Heart Association at Hilton Inn, San Francisco Airport. Thursday-Saturday. Myocardial disease, valvular heart disease, pericardial disease, recent advances in cardiopulmonary disease, coronary disease. \$35. 18 hrs. Contact: Mrs. Frances MacKinnon, Dir., Prof. Ed., 259 Geary St., Room 300, San Francisco 94102. (415) 982-5753.
- October 16—**Clinical Problems in Gastroenterology.** Woodland Clinic Medical Group and Yolo County Chapter, California Academy of General Practice at Woodland Clinic, Woodland. Saturday. \$5. 6½ hrs. Contact: Gerald F. Peppers, M.D., Woodland Clinic Medical Group, 1207 Fairchild Court, Woodland 95695. (916) 662-4641.
- October 16-17—**Pediatric Nephrology.** UCLA. Saturday-Sunday.
- October 20-21—**Dermatology.** USC. Wednesday-Thursday.
- October 20—**Cardiology in the South Pacific.** USC on tour in the South Pacific. Three weeks through November 9.
- October 21-23—**Arthritis.** UCSF and Arthritis Foundation at UCSF. Thursday-Saturday.

October 23—Pathogenesis and Management of Fluid and Electrolyte Imbalance. PMC. Saturday. Third in a series of four workshops. \$50.

October 28—Recent Advances in Kidney Disease. LLU. Thursday. \$25. 8 hrs.

October 28-30—Chest Diseases in Children. UCSF. Thursday-Saturday.

Continuously—Seminar in Clinical and Public Health Aspects of Chest Diseases. Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three hour sessions on fourth Friday of each month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases by instructors and guest lecturers. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—Training of Physicians in Modern Concepts of Pulmonary Care. CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, M.D., LLU.

Continuously—Coronary Care. St. Francis Hospital of Lynwood, Lynwood. Second Thursday of each month, 7:30-8:30 p.m. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—Neurological Sciences. St. Francis Hospital of Lynwood, Lynwood. Fridays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens or current material and review of current topics in specialty. Weekly notification of cases to be available. Contact: Ralph Miller, Director of Education, St. Francis Hospital of Lynwood, 3620 Imperial Highway, Lynwood 90262. (213) 639-5111.

Continuously—Continuing Education in Internal Medicine—Harbor General Hospital. CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12-1 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: Malin Dollinger, M.D., Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

Continuously—Training for Physicians in Nephrology. CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—Training for Physicians in General Internal Medicine. CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—Training in the Procedure of Tonometry. Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California St., San Francisco 94118. (415) 387-0934.

Continuously—Medico-Surgical Cardiovascular Seminar. STAN at Fresno Community Hospital and Valley Medical Center, Fresno. Third Thursday of each month, lectures, demonstrations, seminar discussion, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto VA Hospital, 3901 Miranda Ave., Palo Alto 94306. (415) 326-5600.

Continuously—Cardiology Conferences—CRMP Area III. Second Wednesday monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiologic problems. Contact: William J. Fowkes, Jr., M.D., 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

#### Grand Rounds—Medicine

##### Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

##### Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

Neurology. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

##### Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD

##### Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.



Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## MENTAL RETARDATION

June 21-25—Implications for Future Planning in Mental Retardation: Research and Legislative Changes. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

August 2-11—Community Services for the Mentally Retarded. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. One and one-half weeks. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94104. (415) 848-8281.

September 27—Professional Approaches to Mental Health Services for the Retarded. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Mondays through December 13, 1-6 p.m. 55 hrs. Contact: Portia Bell Hume, M.D., Dir., CTC PMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

October 2-3—Mental Retardation and Autistic Children. UCSF at Napa State Hospital, Imola. Saturday-Sunday.

October 9-22—Mental Retardation. UCLA. Two weeks.

## OBSTETRICS AND GYNECOLOGY

June 18-20—Therapeutic Abortion. PMC. Friday-Sunday. Techniques, social and psychological aspects—counseling, prevention of recurrence, effects on patient and family, attitudes of personnel. \$90.

August 15-18—Fourth Annual Advanced Seminar in Obstetrics and Gynecology. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday. 24 hrs.

September 15-17—Fetal Monitoring. USC. Wednesday-Friday.

September 16-18—Obstetrics and Gynecology Program. UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

October 28-30—Obstetrics Review. USC. Thursday-Saturday.

## Grand Rounds—Obstetrics and Gynecology

### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

10:30 a.m., Auditorium, Womens Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

11:30 a.m., First Floor Auditorium, Room 13-105, UCLA Medical Center. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU

### Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

### Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

### Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

## PEDIATRICS

June 18—Annual Harold K. Faber Day Symposium. STAN and Childrens Hospital at Stanford at Childrens Hospital at Stanford. Friday.

June 23-25—Annual Pediatric Seminar. Childrens Health Center at Sheraton Hotel, Harbor Island, San Diego. Wednesday-Friday. The Preschool Years. \$30. 16 hrs. Contact: David L. Chadwick, M.D., Medical Director, Childrens Health Center, 8001 Frost Street, San Diego 92123. (714) 277-5808, ext. 351.

July 12-14—Chronic Diseases in Childhood. STAN and American Academy of Pediatrics at Childrens Hospital of Stanford, Stanford. Monday-Wednesday. Recent advances in diagnosis and treatment of chronic diseases of childhood, improved techniques for the delivery of health services to children with chronic handicapping conditions. Sections on hematology, allergy, rheumatology, clinical immunology, chest diseases, anesthesiology, psychiatry, genetics, renology, radiology, endocrinology, gastroenterology. Contact: STAN.

July 26-30—Community Health Planning for Services to Children. See Psychiatry, July 26-30.

August 14-15—Armchair Allergy. PMC. Saturday-Sunday. \$55.

September 18—Childrens Hospital Program. UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

October 6-7—Twenty-Eighth Annual Brenneman Memorial Lectures. Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Viral vaccines, viruses and disease, antibiotics, respiratory viral disease, non-bacterial infections of the central nervous system, clinically distinguishable syndromes due to viruses, the abuse of sodium bicarbonate therapy in neonatal acidosis, etiology of hyperbilirubinemia and its management in the neonatal period, differential diagnosis of biliary atresia and neonatal hepatitis, toxicity of phototherapy in neonatal hyperbilirubinemia. Contact: Mrs. Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 753-3704.

October 8-9—Childhood Trauma. Childrens Hospital Medical Center of Oakland at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Carty, Childrens Hospital Medical Center, 51st and Grove Sts., Oakland 94609. (415) 654-5600.

October 9-10—Health of the School Child. UCSF. Saturday-Sunday.

October 16—Childhood and Adolescence. See Adolescent Medicine, October 16.

October 16-17—Pediatric Nephrology. See Medicine, October 16-17.

October 28-30—Chest Diseases in Children. See Medicine, October 28-30.

Continuously—Pediatric Conference. Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. 1 hr. Contact: B. M. Kagan, M.D., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

#### Grand Rounds—Pediatrics

##### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

##### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

##### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

##### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

#### PSYCHIATRY

June 28-July 2—Comparative Psychotherapies. USC Division of Postgraduate Psychiatry at Newport Inn, Newport Beach. Monday-Friday. \$50. 20 hrs. Contact: Donald H. Naftulin, M.D., Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

July 6-16—Life-Crises and Psychiatric Crisis—Intervention. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Two weeks. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

July 19-23—Legislative Issues in Community Mental Health. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

July 19-30—Community Psychiatry and the Law. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Two weeks. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

July 23-25—Workshops in Clinical Hypnosis and Hypnotherapy. American Society of Clinical Hypnosis at St. Francis Hotel, San Francisco. Friday-Sunday. \$125. 22 hrs. Contact: F. D. Nowlin, Exec. Sec., ASCH, 800 Washington Ave., Minneapolis 55414. (612) 331-9452.

July 26-30—Community Mental Health Planning for Services for Children. Center for Training in Community Psychiatry, Los Angeles. Monday-Friday. 35 hrs. Contact: A. R. Beisser, M.D., Dir., Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

August 2-13—Community Resources in Clinical Psychiatry. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Two weeks. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

August 5-12—Somatic Therapy. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. One week. Contact: J. Elizabeth Jeffress, M.D., Chief, Prof. Ed., Agnews State Hospital, San Jose 95114. (408) 262-1200.

August 16-27—Introduction to Mental Health Program Evaluation. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Two weeks. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

August 20-22—International Transactional Analysis Summer Conference. International Transactional Analysis Association at Claremont Hotel, Berkeley. Friday-Sunday. Preceded by introductory course (8 hrs.) in transactional analysis. \$50. Contact: Exec. Sec., ITAA, 3155 College Ave., Berkeley 94705. (415) 653-1420.

September 28—Development of Research Instruments for Program Evaluation. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Tuesdays through December 14, 1-6 p.m. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

September 29—Mental Health Functions of Community Psychiatry. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Wednesdays through December 15, 1-6 p.m. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

September 30—Community Organization for Mental Health. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Thursdays through December 16, 1-6 p.m. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.



October 1—Crisis Intervention, Case-Finding and Habilitation of Handicapped Children and Youth. Center for Training in Community Psychiatry and Mental Health Administration, Berkeley. Fridays through December 17, 1-6 p.m. Contact: Portia Bell Hume, M.D., Dir., CTCPMHA, 2045 Dwight Way, Berkeley 94704. (415) 848-8281.

October 7-9—The Chemistry of Motivation, Mood and Memory. UCSF. Thursday-Saturday.

October 18-22—Group Therapy. UCSF at VA Hospital, San Francisco. Monday-Friday.

Continuously—Eric Berne Seminar of San Francisco. International Transactional Analysis Association at 2709 Jackson St., San Francisco. Tuesday evenings. 8:30 p.m. Contact: Dr. John Dusay, President, 2709 Jackson St., San Francisco 94115. (415) 346-4082.

#### Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

#### RADIOLOGY—PATHOLOGY

June 19-20—Advances in Clinical Enzymology and Other Laboratory Diagnosis. UCLA. Saturday-Sunday.

June 21-26—Pathology of the Lung. UCSD. Monday-Saturday. Pulmonary structure and function in relation to disease, pulmonary anomalies, emphysema, pneumonias, granulomatous diseases, pulmonary circulatory disturbances and vascular disease, hypersensitivity reactions and collagen diseases, neonatal and pediatric pulmonary pathology, tumors and tumor-like conditions of the lungs and pleura, miscellaneous pulmonary diseases of unknown etiology, methods for the study of pulmonary disease. \$200. 48 hrs.

June 27-July 2—Society of Nuclear Medicine. Biltmore Hotel, Los Angeles. Sunday-Friday. Contact: Margaret Glos, SNM, 211 E. 43rd St., New York 10017.

August 3-24—Neuroradiology. Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Tuesdays weekly. 8 hrs. Contact: J. Elizabeth Jeffress, M.D., Chief, Prof. Ed., Agnews State Hospital, San Jose 95114. (408) 262-2100.

October 9—Scintillation Camera Workshop. UCSF Saturday.

Continuously—UCSF Radiology Rounds, Seminars, and Conferences. Weekly meetings October-May. Department of Radiology, UCSF. Open to all physicians without charge. Radiology Chest Conferences, Angiocardiography Rounds, Diagnostic Radiology Seminars, Neuroradiology Seminars, Radiation Therapy Seminars. For schedule information contact: UCSF.

Continuously—Principles and Clinical Uses of Radioisotopes. UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

#### Grand Rounds—Radiology-Pathology

Mondays

Pathology. 12:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Fridays

Neuroradiology. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

#### SURGERY—ANESTHESIOLOGY

June 19—Clinical Electronystagmography Course. Los Angeles Foundation of Otolaryngology. Saturday. Doctors urged to bring ENG technician. Anatomy and Physiology of Vestibular System, Demonstration of Techniques of Vestibular Stimulation and ENG Recording and Calculation, Significance of and Interpretation of Electronystagmogram, Vistas in Vestibular Investigation. \$60. 7 hrs. Contact: Jack L. Pulec, M.D., Los Angeles Foundation of Otolaryngology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

June 24-26—1971 Stanford Ophthalmology Conference. STAN. Thursday-Saturday. Present state of knowledge in fields of ocular motility and ptosis, strabismus. \$125.

July 6—Annual Basic Science Course in Ophthalmology. STAN. Eight and one-half weeks through September 3. Designed primarily for residents. Instruction, lectures and laboratory sessions, emphasis on application of basic science principles to clinical situations and disease conditions.

July 22-30—Pacific Coast Oto-Ophthalmological Society. Royal Hawaiian Hotel, Honolulu. One week. Contact: Francis A. Sooy, M.D., Dept. of Otolaryngology, UCSF.

July 26-28—The Shoulder in Sports. American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. \$150. 24 hrs. Contact: Fred Behling, M.D., 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

August 6-8—Management of Anesthetic Problems in Medical, Obstetrical and Surgical Specialties. UCLA at Neuropsychiatric Institute, UCLA. Friday-Sunday. 9½ hrs.

August 11-15—Advanced Seminars in Urology. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 26-28—Western Section, Association for Research in Vision and Ophthalmology. Western Section, Association for Research in Vision and Ophthalmology at UCSF. Thursday-Saturday. Contact: Robert A. Nozik, M.D., Local Chairman, ARVO, Department of Ophthalmology, UCSF. (415) 666-9000.

September 14—Postgraduate Refresher Course on Orthopaedic Surgical Anatomy (Lower Extremity). Southern California Division, International College of Surgeons at Orthopaedic Hospital, Los Angeles. Tuesday evenings through November 16, 7-9 p.m. Prosections by surgical anatomist, cadaveric surgery, clinical discussions. Enrollment limited to 20. \$120. 20 hrs. Contact: Darline Murphy, Exec. Sec., SCDICS, 136 N. Brighton, Burbank 91506. (213) 846-0669.

September 16—Postgraduate Refresher Course—General Surgical Anatomy. Southern California Division, International College of Surgeons at Orthopaedic Hospital, Los Angeles. Thursday evenings through November 4, 7-9 p.m. Prosections and cadaveric surgery by surgical anatomist, clinical discussions. Enrollment limited to 20. \$100. 16 hrs. Contact: Darline Murphy, Exec. Sec., SCDICS, 136 N. Brighton, Burbank 91506. (213) 846-0669.

September 16—Postgraduate Refresher Course—Surgical Anatomy of the Head and Neck. Southern California Division, International College of Surgeons at Orthopaedic Hospital, Los Angeles. Thursday evenings through November 4, 7-9 p.m. Prosections and cadaveric surgery by surgical anatomist, clinical discussions. Enrollment limited to 20. \$100. 16 hrs. Contact: Darline Murphy, Exec. Sec., SCDICS, 136 N. Brighton, Burbank 91506. (213) 846-0669.

September 19-21—Foot, Ankle and Leg Problems. American Academy of Orthopaedic Surgeons and UCSF at Jack Tar Hotel, San Francisco. Sunday-Tuesday. \$150. Contact: Robert L. Samilson, M.D., 3850 California St., San Francisco 94118. (415) 922-1313.

September 24-25—Vascular Surgery. UCSF. Friday-Saturday.

October 10-14—Western Orthopaedic Association. Century Plaza Hotel, Los Angeles. Contact: Vi Mathieson, Exec. Sec., WOA, 354 21st St., Oakland 95612. (415) 893-1257.

October 15—RX and DX of Knee Derangements. UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Friday.

October 28-30—Strabismus. PMC. Thursday-Saturday.

#### Grand Rounds—Surgery

##### Tuesdays

Orthopedic Surgery. 9:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

##### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

3:00 p.m., Sacramento Medical Center, Sacramento. UCD.

##### Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

##### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stan-

ford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto, STAN.

#### Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

#### OF INTEREST TO ALL PHYSICIANS

##### CMA Postgraduate Institutes and Circuit Courses

June 17-18—Sacramento Valley Counties Regional Postgraduate Institute. CMA, USC and Sacramento County Medical Society at Sahara-Tahoe Hotel, Lake Tahoe. Thursday-Friday. Infections, Immunizations, and Immunology. \$20. Contact: CMA.

June 22—American Association of Medical Clinics—Western Regional Meeting. Disneyland Hotel, Anaheim. Tuesday. Contact: Harold E. Kosanke, M.D., Tucson Clinic, 116 N. Tucson Blvd., Tucson 85702. (602) 327-5531.

June 30-July 4—Eleventh Annual Seminar for General Practitioners. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday. 24 hrs.

July 16-17—Effective Medical Communication. UCLA at UCLA Residential Conference Center, Lake Arrowhead. Friday-Saturday. \$225. 13½ hrs.

August 14-25—Fourteenth Annual Postgraduate Refresher Course. USC at Sheraton-Waikiki, Tripler General Hospital, and Kauai Surf Hotel, Honolulu and Kauai. Two weeks.

August 30-September 2—American Hospital Association. Civic Auditorium, San Francisco. Monday-Thursday. Contact: Edwin L. Crosby, M.D., Exec. Vice-Pres., AHA, 840 N. Lakeshore Dr., Chicago 60611. (312) 645-9400.

September 15-17—Emergency Care. UCSF. Wednesday-Friday.

September 16—Bedside Clinics. USC. Thursday evenings through December 9.

September 21—Emergency Care. USC. Tuesday evenings through December 7.

September 22—Cedars-Sinai Alumni Association Symposium. Century Plaza Hotel, Los Angeles. Wednesday. Contact: Mrs. Barbara Markell, Cedars-Sinai Alumni Sec., Cedars-Sinai Alumni Assoc., 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111.

September 28-29—Computer Program. USC. Tuesday-Wednesday.



October 1-2—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, Exce. Sec., WIMA, 2180 Milvia St., Berkeley 94704. (415) 845-3355.

October 1-2—**Hospital Administration Program.** UCSF. Friday-Saturday.

October 3—**Symposium for Medical Assistants.** UCSF. Sunday.

October 4—**Sex: Past, Present, and Future.** UCSF. Mondays through November 8.

October 5—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings through December 7, except November 9.

October 14-16—**Liquid Scintillation.** UCSF. Thursday-Saturday.

October 16—**Chronic Crippling Disease.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

October 30—**Symposium on Problems Affecting Professional Liability.** Palo Alto Medical Education and Research Foundation and Palo Alto Medical Clinic at Rickey's Hyatt House, San Jose. Saturday. Contact: Kenneth Campbell, M.D., Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto 94305. (415) 321-4121.

October 30-31—**Program at Fresno Community Hospital.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.

**Continuously—Medical Knowledge Self-Assessment Test Review.** PMC. June through October. Review of American College of Physician's last Medical Knowledge Self-Assessment Test. 720 questions to be reviewed. June 19—Gastroenterology, June 26—Cardiovascular Disease, July 10—Endocrinology and Metabolic Disease, September 11—Neurology, September 18—Rheumatology, September 25—Allergy and Infectious Disease, October 9—Hematology, October 16—Renal Disease and Electrolytes.

**Continuously—What's New Series.** Agnews State Hospital and Santa Clara County Mental Health Services at Agnews State Hospital, San Jose. Third Wednesday monthly. Contact: J. Elizabeth Jeffress, M.D., Chief, Prof. Ed., Agnews State Hospital, San Jose 95114. (408) 262-1200.

**Continuously—Basic Science Correlation in Disease.** VA Hospital, Sepulveda. Wednesday evenings, September 16-June 23. Contact: Michael Geokas, M.D., Ph.D., Chief, Medical Service, VA Hospital, Sepulveda 91343. (213) 894-8271.

**Continuously—Educational Tape Service for Orthopaedists, Rheumatologists.** Orthopaedic Audio-Synopsis Foundation. Monthly recorded teaching program on C-60 cassette tapes available to orthopaedic surgeons, rheumatologists and resident physicians. Twelve monthly tapes, annual subscription rate of \$72 (\$50 for residents). Contact J. Tonn, Managing Editor, Orthopaedic Audio-Synopsis Foundation, 6317 Wilshire Blvd., Los Angeles 90048. (213) 986-0131.

**Continuously—Dean's Day Program.** UCSD. One day monthly, 12:30 p.m., Main Auditorium, University Hospital of San Diego County, San Diego. May 27, Anesthesia; June 24, Neurology. Contact: UCSD.

**Continuously—Biomedical Lecture Series.** UCSD. May 19, 8:00 p.m., Basic Sciences Building, UCSD.

**Continuously—Basic Science Lecture Series.** UCSD. Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

**Continuously—Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

**Continuously—Medical Media Network** (formerly Medical Television Network) has discontinued Southern California "scrambled" broadcasting in favor of a film and videotape distribution system. Subscriptions for all California hospitals, rental or purchase. Provides physicians throughout the State with current educational programs in local hospitals. Programs in: Diagnosis of Down's Syndrome, Hemodynamic Monitoring—Intra-Arterial Catheters, Coma, Alcoholism, Malpractice, Emphysema, Food Allergies, The Overweight Patient, Headache. Consult the nearest MNH Hospital regarding time and date for viewing. Programs and study guides developed cooperatively by all California medical schools. Contact: Richard R. Getz, Exec. Dir., MNH, 10962 Le Conte Ave., Los Angeles 90024. (213) 825-2071.

**Continuously—Postgraduate Education Program—Harbor General Hospital.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Practicing physicians invited to participate one-half day weekly over a two-month period in a selected medical or surgical sub-specialty clinic. Patient care, teaching exercises, discussion. Medical clinics currently available: Allergy, Arthritis, Cardiology, Dermatology, Endocrinology, Diabetes, Gastroenterology, Hematology, Neurology, Medical Oncology, Chest, and Renal Hypertension. Surgical sub-specialties also available. Current schedule: June-July, August-September. \$50. 27 hrs. Contact: Malin Dollinger, M.D., Program Director, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1257.

**Continuously—Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, environmental radiation standards and nuclear power plants, overpopulation, abortion and contraception, technological problems of power generation in the United States, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and supersonic transport. Contact: John W. Farquhar, M.D., Assoc. Prof. of Medicine, STAN.

**Continuously—Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.



# Studies on the Nature and Management of Psoriasis

EUGENE M. FARBER, M.D., *Stanford*

■ *Prevalence of psoriasis in Caucasians is estimated as 2 to 3 percent. Sound epidemiologic studies on a worldwide basis are needed to secure accurate prevalence rates for comparative purposes.*

*Utilizing Stanford's psoriasis life histories records, the genetics of psoriasis has been explored by various means: statistical census data, pedigree analysis, and twin studies. This research suggests a multifactorial pattern of inheritance for psoriasis, implying that both genetic and environmental components are responsible for the manifestation of the disease.*

*At present it is not possible to point to any single causative factor. Some of the suggested areas for research include study of uninvolved skin, growth control in the psoriatic lesion, viral causes, immunological aspects, and lipid metabolism.*

PSORIASIS is a common skin disease affecting 2 to 3 percent of the Caucasian population.<sup>1</sup> Although there may be remissions, it must be regarded as incurable by any means now known. Unsightly and disfiguring, the lesions are a stigmatizing blight that causes emotional problems in many, and ruins the lives of persons with severe manifestations. Even persons whose lesions are not conspicuous are not secure, for without warning

they may have severe exacerbations. It is an expensive disease, requiring lifelong treatment and care.<sup>2</sup>

The fundamental defect responsible for the development of the psoriatic lesion is still obscure, even though the literature is full of announcements of findings that are said to be specific. These supposedly definite features have been of various types, and at one time or another have pointed toward a multitude of etiological mechanisms. As time has passed, however, no specific attribute of the disease has been found.<sup>3</sup>

Clinicians have noted that psoriasis increases in severity following a number of phenomena. For example:

- Explosive exacerbations occur following

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**Figure 1.**—A three-year-old male in whom psoriasis appeared after a streptococcal infection of the throat.

streptococcal infections in younger persons (Figure 1). Whyte and Baughman<sup>1</sup> reported that 17 out of 20 patients with acute guttate psoriasis had an antistreptolysin-O (ASO) titer greater than 200 Todd units.

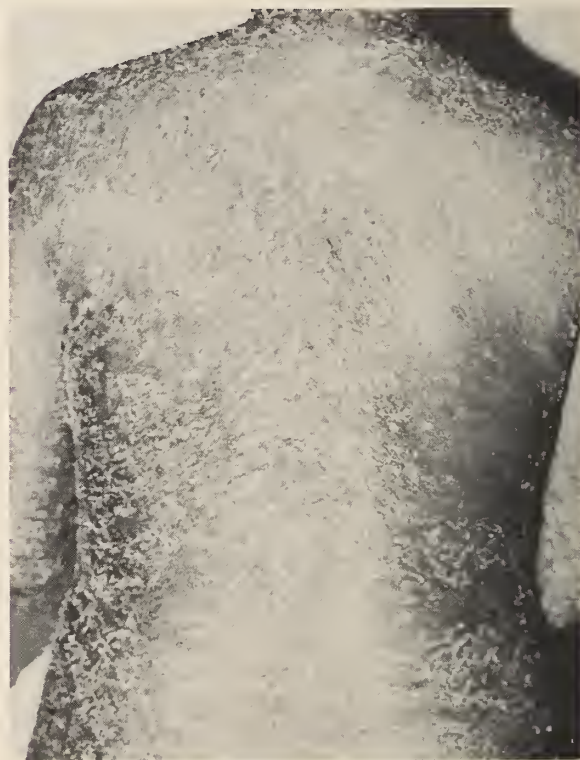
- A person may have minimal psoriasis for ten years or more (Figure 2) and then unaccountably develop severe and widespread psoriasis. A careful history may reveal that the increase in severity of psoriasis, occurring later in the course of the disease, is due to injuries of various sorts to the skin.

- A 28-year-old woman experienced a severe flare of psoriasis after corticosteroid therapy was withdrawn (Figure 3), and a 40-year-old man, who had been receiving Declomycin®\* for a secondary infection developed a phototoxic reaction following sun treatment for psoriasis (Figure 4).

- Rubber, dichromates and, sometimes, formaldehyde—all in the lining of shoes—may produce an inflammatory dermatitis on a contact-allergic basis which may trigger the development of lesions of psoriasis (Figure 5). Ointments



**Figure 2.**—Psoriasis began when the patient was eight years old and lesions were minimal (upper). Severe exacerbations occurred at the age of 18 years following a streptococcal infection (lower).



**Figure 3.**—A 28-year-old woman in whom severe exacerbations of psoriasis occurred after corticosteroid therapy.

\*7-Chloro-6-demethyltetracycline; Declomycin® (Lederle).



Figure 4.—A 40-year-old man, who had been receiving Declomycin® for a secondary infection, had a phototoxic reaction following sun treatment for psoriasis.



Figure 5.—In a 55-year-old man contact dermatitis from lining of shoes aggravated pre-existing psoriasis.

containing sensitizers also may produce isomorphic reactions and new lesions of psoriasis will appear.

## Epidemiology and Genetics

Comprehensive epidemiological studies on the prevalence of psoriasis have been done in the past decade by Hellgren (1967)<sup>5</sup> and Lomholt (1963)<sup>6</sup> in the Scandinavian countries, and by Farber and his associates (1968)<sup>7</sup> in the United States.

Epidemiological studies reveal the frequency of psoriasis in a population and provide information to seek the causative agents for this dis-

ease. Reports in the literature on the prevalence of psoriasis in the general population have been based on the percentage of psoriatic patients found as in-patients or out-patients of hospitals or dermatology clinics.<sup>1</sup>

## Prevalence

Generally, it has been observed that psoriasis occurs with relative frequency among Caucasians, less so in Mongoloids, and rarely in Negroes. In attempting to evaluate the differences in the frequency of psoriasis among different racial groups, Farber, Grauer and Zaruba<sup>8</sup> surveyed racial occurrence in groups throughout the world. They point out that in evaluating prevalence rates the influence of varying factors should be considered: genetics, climate, diet, degree of skin pigmentation, socio-economic background, and the like.

Various observers report the frequency of psoriasis in Caucasians as ranging from 0.1 to 2.84 percent;<sup>1</sup> Farber and Peterson<sup>9</sup> approximate the occurrence of psoriasis at 1 percent to 2 percent in the United States, and if all mild cases were included it might be as high as 3 percent. Psoriasis is more common among the Negroes than is ordinarily recognized. Kenney<sup>10</sup> studied 3,860 diagnoses of consecutive Negro private patients in this country from his dermatologic files. There were 27 (less than 1 percent) with psoriasis. Among 1,230 new patients, belonging to different tribes in Kenya, who had skin diseases 2.6 percent were diagnosed as having psoriasis.<sup>11</sup> It would appear that the occurrence of psoriasis is far higher in Africans than is usually reported. Lomholt<sup>12</sup> indicates that in the Dermatology Clinic of the Mulago Hospital of Uganda, psoriasis is quite common. Although no accurate figures are available, he sees one or two new psoriatic patients each time he visits the skin clinic. He said that the clinical feature is different from that which he observed in Scandinavia. (See Figure 6.)

In personal communications<sup>13</sup> from Indian Service Hospitals in Minnesota, Nebraska and North and South Dakota, ten cases of psoriasis in 38,400 Indians were reported. My only clinical experience with an American Indian with psoriasis was with a 53-year-old full-blooded Apache<sup>\*</sup> man (Figure 7), who had widespread psoriasis.<sup>11</sup> Convit<sup>15</sup> examined 25,915 members of the general population in 95 small rural areas of Bolivia, Ecua-

<sup>\*</sup>Referred by James Arnold, M.D., Medical Officer on the White-river Indian Reservation, Arizona (1968).



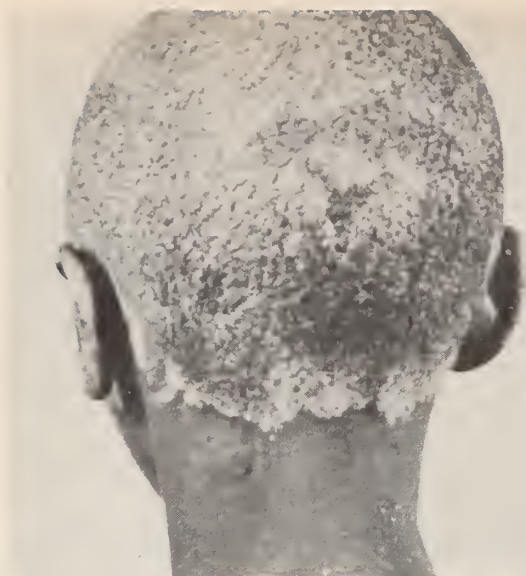


Figure 6.—An African Negro male from Uganda with psoriasis of the scalp. (Courtesy of Gunnar Lomholt, M.D.)

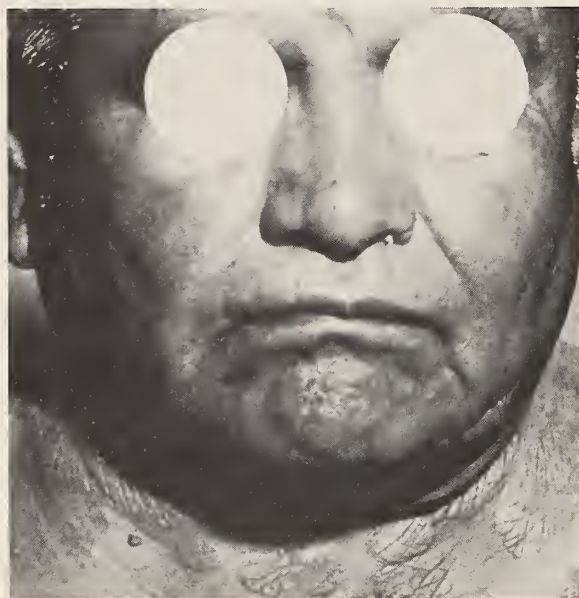


Figure 7.—A 53-year-old male Apache Indian with widespread psoriasis.

dor, Peru, and Venezuela. The locations varied in altitude from the torrid zones at sea level to temperate mountain areas at 10,000 feet. Not a single case of psoriasis was observed in the entire sample.

Psoriasis is said to be less frequent in the Japanese than in Caucasians. Watanabe et al<sup>16</sup> said that before World War II psoriasis accounted for 0.36 percent of all skin diseases in Japan but the incidence had risen to 0.64 percent in 1958. Pre-

TABLE 1.—Percentage of Relatives of Psoriatics who have Psoriasis

Investigator	Psoriasis in families (Percent)	Psoriatics in sample (Number)
Hoede 1931 <sup>19</sup> .....	39	1,437
Hellgren 1967 <sup>5</sup> .....	36	450
Farber et al 1968 <sup>7</sup> .....	36	2,144
Lomholt 1963 <sup>6</sup> .....	91 <sup>a</sup>	312

<sup>a</sup>This is an inbred population.

cise epidemiological data are not available, but Japanese investigators report an increasing prevalence of psoriasis in their country.<sup>17</sup> The increase in the number of persons seeking care in Japan may be directly associated with the improved economic conditions in that country and the greater number of dermatologists in practice.

No cases of psoriasis have been found in native inhabitants of Fiji.<sup>8</sup>

Farber<sup>18</sup> personally examined more than 500 patients in American Samoa and did not find psoriasis in any of them, nor has any physician in practice there reported a Samoan with this disease.

### Genetics

In the Stanford Psoriasis Life Histories Research Unit, approximately 7,000 records of persons with psoriasis are on file. From this file data has been gathered on the occurrence of psoriasis in the families of psoriatic patients. It has long been known that psoriasis "runs in families." Many studies have shown that the prevalence of psoriasis in families of psoriatics is greater than in the general population.

In about one-third of the instances, first, second, and third degree relatives of psoriatics have psoriasis (Table 1).

Familial concentration of a disease raises the question of genetic factors contributing to its manifestation. One can investigate the genetics of a trait by various means including statistical census studies, pedigree analysis, and twin studies.<sup>20</sup>

It is now recognized that many diseases not inherited in a simple manner have some hereditary basis. A genetic component has long been suspected for such conditions as diabetes, rheumatoid arthritis and psoriasis, but genetic analyses do not support inheritance by single gene differences.

Although many investigators agree that the high occurrence of psoriasis in families leads to the assumption that genetic factors play an etiologic

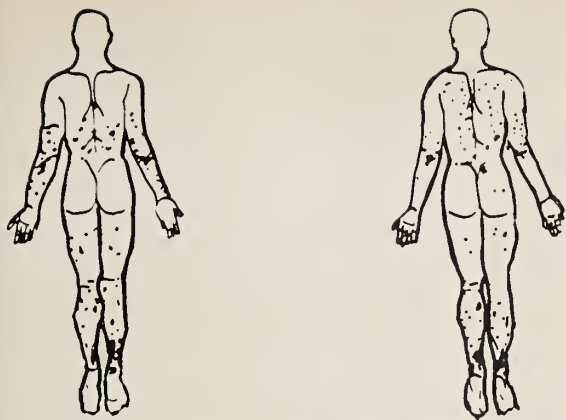


Figure 8.—Schematic illustration of geographic distribution of psoriasis in 18-year-old monozygotic male twins, showing similarity of pattern.

role, there is no agreement on the mode of inheritance. The interpretation of the observations ranges from simple dominance to digene recessivity.<sup>21</sup>

The prevailing theories of the modes of inheritance of psoriasis are:

- simple autosomal dominant with incomplete penetrance;
- double autosomal recessive;
- multifactorial.

Farber and Nall<sup>22</sup> in reviewing data on 40 pairs of monozygotic twins, noted that 27 pairs were concordant for and 13 pairs were discordant for psoriasis. Of 39 pairs of dizygotic twins, nine were concordant and 30 discordant. That not all monozygotic twins were concordant would indicate that other factors—environment, for example—are also influential. Why 13 of the monozygotic twin pairs were discordant for psoriasis requires careful study and analysis.

There are several pairs of both monozygotic and dizygotic twins in our different population samples. Two male monozygotic twins developed psoriasis at the same time with similar patterns of coverage over the surface of the body area (Figure 8). Zygosity diagnosis revealed they had identical blood types.

In a study of 698 probands with psoriasis, Watson et al<sup>20</sup> found from a mating analysis that:

- a) there were 1,089 siblings from families in which neither parent had psoriasis; 7.8 percent of these siblings had psoriasis;
- b) 16.4 percent of the siblings (256) had psoriasis when *one* parent was affected;
- c) 50 percent of the siblings (12) had psoriasis

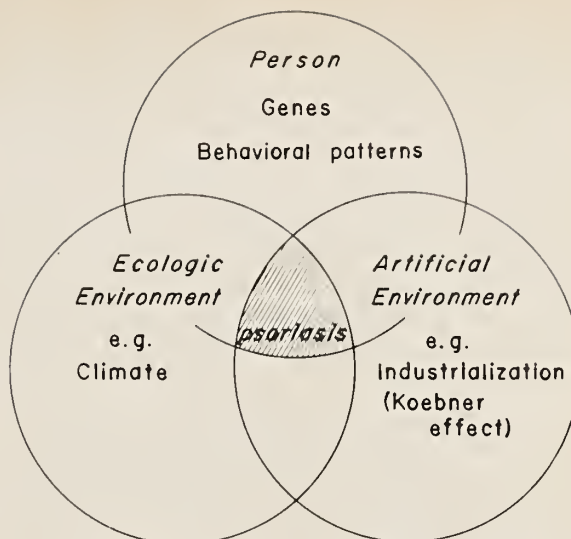


Chart 1.—A Venn<sup>23</sup> diagram illustrating the interaction of genetic and environmental components. The intersection of the three circles represents the presence of psoriasis. The top circle represents the person himself with a genetic and behavioral predisposition for psoriasis and the other two circles represent factors in the natural and artificial environments that precipitate the psoriatic lesion.

when *both* parents had psoriasis. (It should be noted that the last figure is too small a sample to be statistically significant.)

In autosomal dominant inheritance, 50 percent of the siblings from one affected parent would be expected to have psoriasis. In autosomal recessive inheritance, one-quarter of the siblings of probands would be expected to be affected if neither parent is affected, and all of the siblings when both parents are affected.

Our figures are much lower than those expected from simple autosomal dominance and recessivity or sex-linked inheritance, and the mode of inheritance cannot be explained by any of these.

Our family studies would suggest a multifactorial pattern of inheritance for psoriasis. This implies that multiple genes and environment are responsible for the clinical appearance of the disease. The concept of genetic and environmental components interacting in the manifestation of psoriasis is illustrated in Chart 1.

## Suggested Fields for Psoriasis Research

Psoriasis, like many another disease, has remained an enigma. The cause is unknown. The factors which are known are: the skin is the only tissue involved; there is a familial-genetic background; lesions are symmetrical; nails are in-



volved; there is no diagnostic test; there are no metabolic abnormalities; and injury to the skin can precipitate a psoriatic lesion.

Psoriasis is characterized by thick lesions covered with scales; there is much mitotic activity in the epidermis as well as accelerated chemical processes. Parakeratosis, vascular changes, and inflammation are thought to be secondary phenomena. Rapid epidermal cell growth is due to rapid cell turnover, but this is not qualitatively different from other types of rapid epidermal growth.

At present it is not possible to point to any single causative factor. Therefore, it is essential to review every possibility for this particular growth disturbance. Some fields of investigation are more promising than others:

### *Study of Uninvolved Skin*

Study of the predisposed, but uninvolved, skin in psoriasis (particularly in the early stages of evolving changes) is more likely to yield information concerning the nature of the psoriatic process than could be expected from further study of psoriatic plaques themselves. The cause should be sought in a deviation of the growth-control mechanism rather than in the rapidly growing epidermis *per se*.<sup>24</sup>

If it is possible to identify the presence of some predisposing feature of the symptom-free skin in patients destined to have psoriasis, it will open the door to significant research.

There is no animal model for psoriasis. An appropriate human model for the study of psoriasis is the patient himself. The symptomless skin of a psoriatic patient can be used for research by inducing lesions through experimental injury.

### *Growth Control in the Psoriatic Lesion*

Psoriasis is a disturbance characterized by the rapid growth of epithelial tissue. All palliative therapy is designed to keep epidermal growth at its normal level, whereas curative therapy is designed to restore normal growth control. Not known is how the growth control is operative or where it is located. Therefore, research cannot be narrowed down too much, because many areas remain to be explored.

When normal skin is stripped with Scotch tape, its epidermis grows faster, indicating that a regulating factor has been removed.<sup>25</sup> What keeps

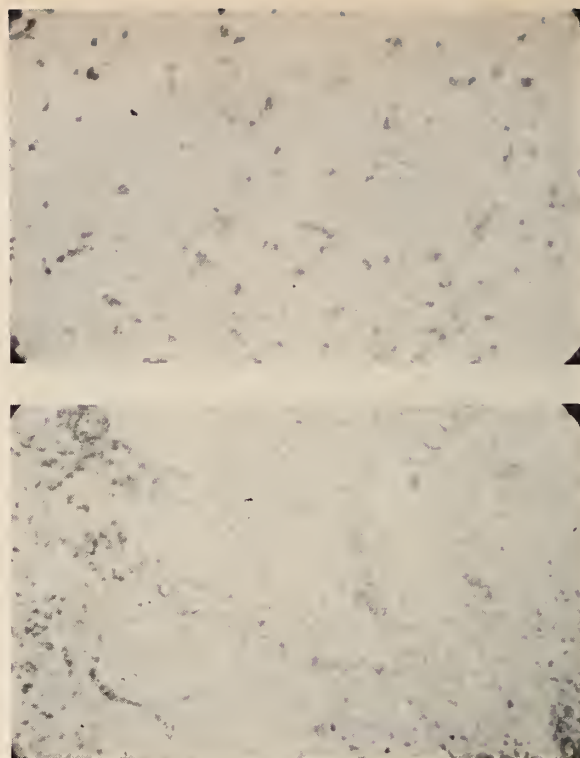


Figure 9.—Epidermal cell growth. Top frame shows control in which isolated epithelial cells were grown in standard media for five days. Lower frame shows epithelial cells grown in conditioned media from rabbit dermal fibroblasts for five days.

normal epidermis in check? In psoriatic patients, injury to symptomless skin triggers epidermal growth that continues longer than that of normal epidermis following injury. This isomorphic response can be used as a model to study the evolution of the psoriatic lesion, by histologic means or measurements of the variety of biochemical changes in the evolving lesion.

Useful information may be provided by detailed studies of the nucleus in symptomless skin, using quantitative histochemistry or autoradiography for early changes in deoxyribonucleic acid (DNA) synthesis in evolving lesions.<sup>26</sup>

Feedback inhibition of DNA synthesis by end-products of nucleic acid metabolism is a possibility that needs exploration. The induction and repression of enzymes of nucleotide synthesis in the basal cell population, and the allosteric control of DNA and ribonucleic acid (RNA) synthesis are approaches that properly could be applied to the skin epithelial cell.

Karasek<sup>26</sup> has studied the role which the dermis plays in the regulation of epithelial cell growth. The top photograph of Figure 9 shows a control

in which isolated rabbit epithelial cells were grown in the presence of the standard media for five days. In the lower photograph are epithelial cells grown in the presence of conditioned media from rabbit dermal fibroblasts for five days; the initial growth of the control slide has stopped. While in the presence of conditioned media, growth was definitely stimulated.

To clarify this phenomenon in relation to psoriasis, study of the isolation and characterization of the cues produced or stored by the dermis should be undertaken, and an analysis of the way in which these cues interact with the epithelial cell to increase or repress mitosis should be made.

It can logically be argued that epithelial growth response in psoriasis is a result of dermal factors. This is a field for useful future research in psoriasis.

### *Viral Research*

There is evidence that viruses cause disturbances in cell growth, and that they modify or control cell growth.<sup>27</sup> If there is a virus in psoriasis, it has not been identified. A case can be made for the possibility of a viral factor in psoriasis. One could postulate a viral DNA as well as a tissue DNA existing in the cell nucleus, with the former modified by successful treatment, the mammalian DNA continuing to function with resumption of normal cell growth.

It is well known that heat or light activates herpes simplex virus. Is this a Koebner reaction? In psoriasis, injury or environmental changes may result in a Koebner reaction. Is the isomorphic response in psoriasis a result of a virus-provoking cause?

### *Immunologic Aspects*

There is no clear-cut evidence to support an immunologic basis for psoriasis, though several reports in the literature have pointed to a possible immunologic disturbance.<sup>4,6,28</sup>

In the Stanford Psoriasis Questionnaire Survey of 2,144 psoriatic persons,<sup>7</sup> 14 percent indicated that they had had either asthma or hay fever—about the same prevalence as for atopy in non-psoriatic persons.

Immediate hypersensitivity in patients with psoriasis is no different from that in controls, and there is no hard evidence for differences in delayed hypersensitivity.

In support of immunologic factors are some clinical observations such as the appearance of guttate lesions after streptococcal infection, and remission following measles.<sup>4</sup>

There have been several reports of measles altering the course of psoriasis. Lomholt<sup>6</sup> investigated the effect of measles on psoriasis and found cases of severe guttate eruptions of psoriasis following measles. He also found, however, complete disappearance of psoriatic lesions in seven patients during and following measles. This led to speculation by some observers that immunologic factors might play a role in the pathogenesis of psoriasis, since the lymphoid system is somewhat depressed during infection with rubeola.

There is insufficient information about possible defects in the cellular immune response or the mediators of inflammation. Such studies should be carried forward with the most modern and sophisticated of methods.

### *Lipids*

Is there a case for faulty lipid synthesis? At present, changes in membrane structure are thought to be responsible for the abnormal behavior of many types of cells.<sup>29</sup> (A defect in the cell membrane structure includes the outer membrane as well as the internal membranes of the endoplasmic reticulum.)

These membrane changes can be induced by viruses or by a variety of chemicals. Rubin's concept<sup>30</sup> of carcinoma cells is related to the synthesis of abnormal protein in cells that changes the cell membrane and cell growth.

Whether or not there is a defective membrane synthesis in psoriasis deserves a careful look.

### *Treatment*

Psoriasis requires treatment because of pruritis, disfigurement and frequently pain. Treatment is very often symptomatic. More recently, fundamental science has been reflected in varying forms of experimental therapy. It is conceivable that with much research effort, a specific agent could be found which, when applied to the lesions, would control psoriasis much as insulin controls diabetes.<sup>29</sup>

An effort should be made to find antimetabolites which will have a suppressive effect on psoriasis without the hazards of toxicity associated with systemic administration. Since psoriasis and can-



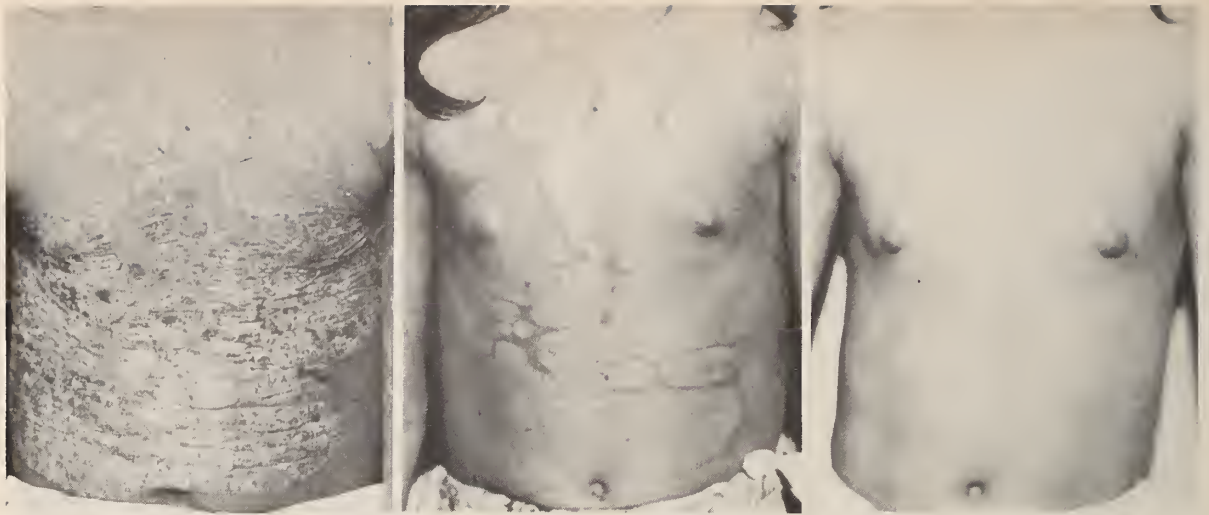


Figure 10.—Psoriatic lesions before treatment with anthralin (left) one week later (center) and three months later.

cer have the common characteristic of cellular hyperplasia and increased metabolic and mitotic activity, antimetabolites successful in controlling cancer should be tried in psoriasis.

When a distinct suppression of the psoriatic process is noted from the application of a test substance, a detailed analysis of the mechanism involved should be performed. These could include electronmicroscopy, tritiated thymidine uptake, p-32 uptake, and mitotic counts, before and after therapy.

The finding of a practical, non-toxic and effective topical treatment would be of immeasurable benefit to the estimated 4 to 6 million patients in the United States who have this chronic skin disease.

Available now are only a few drugs—all palliative, and all involved with side reactions:

**Crude coal tar, Anthralin, corticosteroids, retinoic acid**

**5-fluorouracil, 6-mercaptopurine, 6-diazo-5-oxo-L-norleucine, hydroxyurea**

**Actinomycin D, Puromycin, Podophyllin**

There is hope, through proper studies, of improving the situation. Anthralin, for example, is a drug that has been long known but not sufficiently appreciated.<sup>32,33</sup> The relapse rate, however, is nearly 100 percent; and the treatment is messy and irritating (Figure 10). Nonetheless, it is extremely effective when applied carefully and under supervision.

Crude coal tar has been widely used in the treatment of psoriasis for more than 50 years. In these before-and-after photographs (Figure 11) a striking remission is seen; but almost all patients relapse, and not all do as well as the patient shown.

Another patient was treated on her left side with an aqueous solution of 0.05 percent nitrogen mustard,<sup>34</sup> applied daily for ten days to a small area of psoriasis on her back (Figure 12). The treated area completely cleared. However, 90 percent of patients treated with nitrogen mustard have severe reactions of delayed hypersensitivity if treatment is continued. The drug is also potentially toxic and, therefore, not suited to general use. A search for a non-toxic drug for psoriasis should continue with undiminished energy.

## Conclusion

As new advances are made in the basic biology of cell growth, there will be a greater understanding of ways of controlling the rapid epidermal cell growth that is characteristic of psoriasis.

To solve the problem of psoriasis, it is probably necessary to:

- Develop interdisciplinary studies involving dermatologists, skin biologists, pharmacologists, and other basic scientists.
- Establish psoriasis centers that could participate in research with other medical institutions as well as with each other. Centers for psoriasis could act as a resource for a region of the country.



Figure 11.—Psoriatic lesions before treatment with 2 percent crude coal tar in an ointment base (left) and six weeks after treatment.



Figure 12.—Psoriasis treated with nitrogen mustard. This photograph taken three months after a ten-day course of treatment shows clearing in the treated area.

Their expertise in the clinical care, research, and education should link them with all dermatologists in their area. Such centers can provide information for all dermatologists who wish to visit and learn. Cooperating psoriasis centers and dermatologists can share in on-going research and have available the reports of their findings before publication.

The resources in support of psoriasis research today are insufficient. More investigators and funds are needed, for without both, research ideas cannot be implemented.

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## ON WITHDRAWING STEROIDS

In patients with chronic ulcerative colitis who have been on steroids for more than five years, how soon after surgery do you stop the medication?

"I would suggest first that if you have to treat patients with steroids for long periods of time, you should use the medication every second day and allow a day for the adrenals to escape at least partially. In that way there is less adrenal suppression. In other words, if you plan to use 15 mg of prednisone a day, use 30 mg every second day instead. I see no difference in the control of the patient.

"Patients who take steroids for a prolonged period of time must be taken off very slowly, indeed. Perhaps these patients should have an ACTH stimulation before they are taken off and perhaps they should even have adrenal function studies, too. I think that you would be talking about a period of weeks. I would tend personally to taper patients off very slowly and watch them very carefully over a period of many weeks. If they were taking 20 mg of prednisone a day, I would cut the dosage down by no more than one tablet each month. If there were any suggestion of difficulty, I would stop and do adrenal function studies and be certain that the adrenals were able to respond."

—F. WARREN NUGENT, M.D., Boston

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# Abdominal Aortic Aneurysmectomy, 1968-1969

## A Review of Recent Experience of the Southern California Permanente Medical Group

DANIEL DEVOR, M.D., *Fontana*

■ *Seventy-three aneurysmectomies were done in the two-year period 1968-1969 for a Health Plan population of 771,000. The mortality in the elective cases was nine percent and in the emergency cases 44 percent. An analysis of the complications and causes of death reveals them to be essentially the same as reported by others. Bleeding and myocardial infarction are the two most common causes of death in emergency operations. Pneumonia and urinary tract infections are the most common complications in successful cases.*

*Comparison of this report of recent experience with reports of cumulative series is difficult. The morbidity and mortality reported here is felt to be representative of current practice.*

THE SOUTHERN CALIFORNIA PERMANENTE MEDICAL GROUP's combined experience in the surgical management of aneurysms during the years 1968 and 1969 has been reviewed. This experience is unique in that we are a hospital system serving a large, controlled population. Rarely are cases referred to university centers or specialty hospitals. Our experience is a reasonable standard for comparison with community hospitals.

Aneurysmectomy was done in 73 cases in an average Health Plan population of 771,000 during the two-year period from January 1, 1968 through December 31, 1969. In 18 emergency cases there were eight deaths, and in 55 elective

cases five deaths. There was pronounced variation in the incidence of surgical treatment of aneurysms by hospital area, probably reflecting differences in age groups (Table 1). The operations were performed by ten surgeons working in five hospitals. No surgeon had more than two unsuccessful elective cases.

Patient age ranged from 50 to 83 years and averaged 66 years (Table 2). There was no significant difference in the average age of those with elective and emergency operations. The average age of all surviving patients was little different than the overall age. The only significant deviation from this pattern was that those dying after elective operation tended to be about seven years older than the survivors of elective resection.

Of the 73 patients, five were women and their

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average age was 62. Two of the five had ruptured aneurysms and one of those died.

There were 33 patients of working age in the group—men less than 65 and women less than 62. Twenty-seven of them are known to have been working preoperatively. Postoperatively, 19 are known to have resumed work, four retired, three were dead and one is lost to follow-up. There was no apparent relationship between the patient's occupation and his disease or the outcome of operation.

## Discovery

Elective cases were discovered in a variety of ways and classification into neat categories is difficult. Four were discovered as a result of laparotomy for other conditions. Four were discovered during an evaluation for vascular disease. The remainder were about equally divided between incidental x-ray diagnosis, routine physical examinations of asymptomatic patients, and evaluation of symptomatic patients. The executive physical examination at the Fontana Kaiser steel mill includes a routine lumbosacral spine film. Three cases in this two-year series were diagnosed by this means.

Ruptured aneurysms were discovered because of shock, syncope, or pain which precipitated emergency evaluation. There were three exceptions: In one patient with a previous graft an aorto-duodenal fistula developed and investigation was carried out because of "gastrointestinal bleeding"; another presented with vomiting; in the third operation was done as an elective procedure but the patient was found to have had a spontaneous rupture.

## Incidental Findings

Incidental findings in 73 operations were three cases of gallstones and a renal cyst. There was no malignant disease discovered at operation. In several cases the operative report remarked on the extensive (and previously unrecognized) vascular disease.

## Accessory Procedures

Procedures that are not normally a part of the basic aneurysmectomy and graft replacement have been defined as "accessory procedures"

**TABLE 1.—Cases by Hospital and Incidence for 10,000**

Total	73	0.945
Fontana	21	1.99
San Diego	7	1.77
Sunset (Los Angeles)	28	0.97
Harbor	8	0.86
Bellflower	4	0.40
Panorama	5	0.37

**TABLE 2.—Ages of Patients with Operation for Aneurysm**

	Average Patient Age 66.0	
	Elective	Ruptured
All	65.8	66.3
Survival	65.5	65.6
Death	72.8	67.0

**TABLE 3.—Accessory Procedures**

Gastrostomy	5
Renal artery operation	3
Renal exploration	2
Hernia repair	2
Sympathectomy	1
Appendectomy	1

(Table 3). There were 14 such procedures performed (12 in elective cases and two in emergency cases). Six were done by one surgeon in the first year of the study period; he did no accessory procedures thereafter, although no mortality or morbidity was associated with them. He did four of the five gastrostomies, a hernia repair, and the appendectomy. None of the procedures resulted in death or complication. The nine cases of pneumonia in this series includes one in which gastrostomy had been done. Renal exploration and arterial operations are understandable in view of the exposure during aneurysmectomy and the natural course of those operations. Many aneurysms come to resection as an outgrowth of renal or renovascular evaluations.

## Secondary Procedures

Secondary procedures were defined as procedures necessary to correct some condition arising as a result of operation. There were ten such procedures performed on nine patients—all but

one in elective cases. The most common was reoperation for bleeding detected in the early postoperative period. Operations for bleeding were performed in one emergency case and three elective cases. Only in the single case where the bleeding did not arise as an artifact of operation did death ensue.

Thrombectomy was done successfully in three cases. There was no limb loss or chronic ischemia following operation. Tracheostomy and insertion of a pacemaker was done for a patient who had a chronic arrhythmia and in whom pneumonia developed. Gastrostomy was done in an elective case and the patient died.

Blood Replacement

In elective operations, average blood replacement during operation was 4.5 units. Survivors received an average of 3.8 units. Five successful operations were done without the administration of any blood; three patients were given only a single unit and only three received eight or more units. In the five unsuccessful elective cases, blood loss averaged more than twice that for successful elective cases. One patient received 30 units but even excluding this case the average was 6.7 units—well above average blood replacement for elective operations (Table 4).

Large volume blood replacements was consistently associated with emergency operations regardless of the outcome. Replacement averaged 7.3 units. All required blood and the minimum amount given (4 units) in successful cases exceeded the average in surviving elective cases.

Postoperative Stay

Surviving patients with elective operation had a significantly lower complication rate than those who had emergency operations. This was reflected in the duration of postoperative stay. In elective cases postoperative care averaged 9.8 days and the complication rate was 26 percent. In emergency cases postoperative care averaged 11.1 days and the complication rate was 67 percent (Table 5). The shortest stay in an elective case was six days. The longest stay was 36 days, 34 of them postoperative. The patient in that case had a multiplicity of complications including delirium tremens, pulmonary edema and stroke, but he recovered and returned to work.

Postoperative Complications in Successful Cases

The 32 complications which occurred in the 60 successful cases were those expected in any major geriatric surgical group plus those inherent in vascular surgery (Table 6). Those complications occurred among 24 patients. Only one patient had more than two complications.

Pneumonia was the most common postoperative complication. A tracheostomy was done once as an adjunctive treatment measure.

Urinary infection was the second most common complication. An in-dwelling catheter is standard practice in aneurysmal surgery. The three-way antibiotic-irrigated catheter was not used in any of these cases and prophylactic antibiotics were not used for urinary infection.

Embolism and thrombosis occurred in four cases but embolectomy was done in only two.

TABLE 4.—A Comparison of Total Operative Blood Replacement in Elective and Emergency Cases

Elective	Units	Range
Survived	3.8	0-17
Died	11.4	3-30
Emergency		
Survived	7.3	4-13
Died	7.3	2-19

TABLE 5.—Average Total Stay in Hospital

All Cases	11.9 days
Non-surviving	7.5 days
Surviving	
Emergency	14.3 days
Elective	12.5 days

TABLE 6.—A Summary of Complications in Successful Cases

(32 Complications in 60 Successful Cases)	
Pneumonia	8
Urinary infection	5
Embolism and thrombosis	4
Ileus	3
Confusion	2
Wound infection	2
Cardiac	2
Urinary obstruction	2
Bleeding	1
Electrolyte imbalance	1
Delirium tremens	1
Cerebral vascular accident	1



One of the four had pain in the right great toe immediately after operation. The toe turned black, gradually the pain left and, at the end of about two weeks, the entire outer layer of skin came off as a mummified cast, revealing a healthy pink toe. In the fourth case a graft limb failed to remain patent after operation but no further effort was made.

Only two patients required reoperation for bleeding. Unusually prolonged ileus was recorded in three cases, and this resulted in prolongation of hospital stay. Each of the other complications was relatively rare.

Ventral hernia was noted in one case but this is not a reliable estimate of the incidence of this complication. The cases in this review are all from recent experience and do not reflect long term follow-up and unbiased observation by disinterested observers.

Jaundice was noted in two patients as a transient postoperative complication. The cause of this jaundice was not investigated sufficiently to allow evaluation. It resolved rapidly and spontaneously in both cases.

The average duration of anesthesia was 240 minutes. Pneumonitis occurred in only one case in which anesthesia lasted less than this time. Cases of especially long duration also had a low incidence of pneumonia and atelectasis. This study cannot identify all of the factors involved in this preventable complication but it suggests that anesthetic and postanesthetic management of pulmonary toilet must be especially vigorous in prolonged cases.

## Deaths in Elective Cases

The cases of the five patients who died following elective resection deserve special review:

*Case 1.* The patient was a 69-year-old man who underwent elective resection of an aneurysm that was symptomatic but unruptured. The total anesthetic time was short (two and a half hours) and the blood losses were moderate (4 units were given during operation). He appeared to do well until he showed evidence of acute blood loss on the fourth postoperative day. At reoperation, he was found to have a ruptured hepatic artery aneurysm and he died shortly thereafter.

*Comment:* This unexpected death cannot be attributed to surgical error but is due to random

accident. It is of interest that the vascular accident occurred during a postoperative period when even hypertensive patients are frequently normotensive.

*Case 2.* A 77-year-old retired man was found to have an aneurysm during a routine examination. The operation was evidently difficult, for it lasted 6 hours and 55 minutes. Thirty units of blood were administered during the procedure. Bilateral iliac artery aneurysms were also resected and a bifurcated graft was inserted. The patient gradually recovered and he was discharged to home on the 22nd postoperative day. Four days later he died. At autopsy, the suture line was found to be disrupted in a peculiar way. The suture was tied and the tissues sound; the suture was broken at midpoint.

*Comment:* The surgeon was firm in his belief that the failure was due to defective suture. The suspicion remains that this suture failure arose from mishandling of the material by some member of the team. A clamp momentarily applied to suture can cause later failure.

*Case 3.* A 77-year-old retired man with significant cardiac disease underwent elective resection for a massive aneurysm in intimate contact with the pancreas. The operation was technically difficult and prolonged. Ten units of blood were given during the course of a six-hour procedure. The patient died on the eighth postoperative day of renal failure secondary to severe pancreatitis.

*Comment:* This technically challenging procedure was undertaken by a team of surgeons who had not operated together before. The pancreas is ever a hostile organ for the surgeon, and massive aneurysms require coordinated and proficient team surgery. Retreat, in such circumstances, is an indication of mature surgical judgment.

*Case 4.* In a 72-year-old man a large aneurysm was discovered during an excretory urogram. Operation was prolonged by the presence of massive iliac aneurysms. Anesthesia lasted four hours and 50 minutes, and 10 units of blood were given. The patient did poorly postoperatively and it gradually became evident that although he was entirely afebrile pneumonia had developed. He died on the eighth postoperative day of staphylococcal pneumonitis.

*Comment:* The patient died because of failure

to recognize an insidious respiratory problem. The elderly and the debilitated are capable of atypical response to infection and this must be constantly borne in mind when dealing with geriatric patients.

*Case 5.* A 74-year-old man complained of a pulsating mass in the abdomen. He had an uneventful resection of moderate duration. Three units of blood were given. He did well until the early hours of the fourth postoperative day, when he went into shock and was thought to have had a heart attack. He was given a moderate amount of intravenous fluids and he spontaneously improved. Within two hours he was alert, normotensive and apparently stable. It was elected to observe him carefully for the remainder of the day. He continued to improve that day but he gradually deteriorated during the next several days. At autopsy, he was found to have had a suture-line leak, tamponade of major vessels and secondary renal, hepatic and intestinal failure.

*Comment:* Patients who have the sudden onset of shock after vascular operation, then a period of apparent stabilization, should be considered to have had a vascular disruption. There is a transient period in which successful repair can be done, and failure to recognize the significance of this pattern of events is serious error.

In summary, of the five cases in which death occurred, only one was entirely without an element of technical diagnostic error. All would require early and aggressive management for a successful outcome.

Deaths in Emergency Cases

Three of the deaths from ruptured aneurysms deserve special comment. Those who die after rupture of aneurysms appear to present special and formidable problems (Table 7).

*Case 1.* A 61-year-old man had had two myocardial infarcts within the previous 15 months and he was diagnosed as having generalized arteriosclerotic heart disease. He was in hospital for two days with what was thought to be acute pain from a ureteral calculus. Only when he went into frank shock was his problem finally recognized. He died at operation despite rapid transfusion and an effort to control the hemorrhage.

TABLE 7.—Causes of Death in Emergency Cases

Uncontrolled bleeding at operation .....	3
Postoperative myocardial infarction .....	2
Acute bleeding diathesis .....	1
Colonic slough .....	1
Moribund before operation .....	1

*Comment:* This inherently poor-risk patient arrived in the operating room in a moribund condition because of an error of diagnosis. There is little or no hope of salvage in such cases.

*Case 2.* A 65-year-old man was seized with severe abdominal pain early one morning. He ate a hearty breakfast and did some exercises to work out the pain. He finally collapsed and was brought to the hospital by ambulance. He was known to have chronic renal disease and hypothyroidism. At operation aneurysm was repaired and relatively advanced cirrhosis of the liver was found. He did poorly and a bloody diarrhea developed shortly before he died.

*Comment:* This patient behaved in a way occasionally seen in myocardial infarction cases. His efforts to eat and exercise his discomfort away, preoperative shock, and chronic ill health made him an exceptionally poor risk. Ischemic colon made death inevitable.

*Case 3.* An 80-year-old diabetic man was operated upon in emergency. He had a satisfactory graft replacement and then bleeding from all cut surfaces began abruptly. Massive transfusions were ineffective and despite infusion of 19 units of whole blood he died of exsanguination.

*Comment:* Sudden hemorrhage after multiple transfusions is apparently initiated by some ill-defined lytic mechanism. Administration of fresh whole blood or amino caproic acid are the treatments of choice.

Those three examples are representative of the more difficult problems that are associated with ruptured aneurysms. Little blame can be laid to the surgeons for the deaths in those cases.

Comparison of Experience

Mortality in elective aneurysm resection has unquestionably decreased substantially during the past five years. In the Rochester series the



**TABLE 8.—A Comparison of Experience in Present Series with Recent Reports from the Surgical Literature**

<i>Recent Reports</i>		
<i>Elective Abdominal Aortic Aneurysms</i>		
	<i>Cases</i>	<i>Mortality (Percent)</i>
So. Cal. Permanente .....	55	9.1
Charlotte <sup>1</sup> .....	150	6.7
U. Rochester <sup>2</sup> .....	—	9.8*
Navy, San Diego <sup>3</sup> .....	57	17.5
*13 percent, 1955-65; 9.8 percent, 1961-65		
<i>Ruptured Abdominal Aortic Aneurysms</i>		
	<i>Cases</i>	<i>Mortality (Percent)</i>
So. Cal. Permanente .....	18	44
St. Luke's, Chicago <sup>4</sup> .....	107	54
U. Rochester <sup>2</sup> .....	41	69
Navy, San Diego <sup>3</sup> .....	11	82
L.A. County <sup>5</sup> .....	41	83

rate dropped dramatically (from 13 percent to 9.8 percent) during the last four years of their reporting period. The 9.1 percent rate in the series herein reported can be considered as hopeful but possible to improve (Table 8).

The mortality in the management of ruptured aneurysms was tabulated in a recent review by

May, DeWeese, Frank, Mahoney and Rob. There has been no pronounced improvement in the mortality rates as reported in the last ten years. The raw figures are deceptive in that most of the reports concern ongoing series that reflect cumulative rather than recent experience. The St. Luke's report is a 15-year accumulation; Rochester's ten years; Navy's six years; Los Angeles County's ten years. The relatively low mortality in our small series probably is a reflection of current practice. As our data indicate, availability of blood, good anesthetic management, and postoperative care of complications are all factors critical in the care of these patients.

The mortality rate reported here in emergency cases (44 percent) is felt to reflect current practice and an acceptable level of performance.

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#### SEAT BELTS AND FACIAL INJURIES

"Acute trauma to the larynx and midface is becoming an increasingly common problem, occasioned mainly by the use of automobile seat belts (especially the lap belts). Whereas people used to be killed by being hurtled out through the windshield, they are now being retained in the vehicle with the lap belt. When the car decelerates, the head and trunk of the body are propelled forward in jack-knife fashion so that some part of the upper anatomy usually encounters either the steering wheel or the dashboard. If the head is flexed when it goes forward, the major injury will be to the face; if it is extended, the injury will be mainly to the larynx. There certainly appear to be enough skinny people, women with long slender necks without strong musculature and men of the same build, so that laryngeal fractures and trauma are becoming much more common...."

—GEORGE F. REED, M.D., Syracuse

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# The Role of Phagocyte Function in Resistance to Infection

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MORE THAN ONE generation of physicians has placed its faith in "the Lord and the leukocytes" when visiting the sickbed of a patient with infection. Although the continued interest of the Lord has been questioned by some, and reinforced with antibiotics by others, phagocytic leukocytes remain a major determinant of our ability to survive exposure to pathogenic microorganisms. Recent investigations have increased our knowledge of the phagocytic process, and have led to the finding that several disorders of man are caused by or associated with defective phagocyte function. This paper will review some of this new information, especially as it relates to the function of phagocytes in human illness. The interested reader will find additional details in recent publications.<sup>1-3</sup>

## Life Cycle of Leukocytes

Of the several types of phagocytic leukocytes, neutrophils have received the most extensive study. In structure and function this cell type shows numerous adaptations that equip it to respond rapidly and effectively to tissue invasion by microbes. The circulating pool of neutrophils, estimated roughly by a routine white blood cell count and a differential count, is continuously re-

newed by neutrophils that enter the blood from the bone marrow at a rate of 80 million cells per minute in the "average" adult.<sup>4</sup> This freely circulating pool is in equilibrium with an approximately equal number of mature neutrophils within the vasculature of certain organs. The latter are able to enter the circulation in response to various hormonal or metabolic stimuli.<sup>4,5</sup> Normally, at least four days elapse after the last occurrence of deoxyribonucleic acid (DNA) synthesis in a marrow precursor before the appearance of neutrophils in the circulation, but this may be considerably shortened in patients with acute infections and leukemoid reactions.<sup>6</sup> Under normal conditions, the half-time of a neutrophil in the peripheral blood of man is estimated to be approximately six and a half to seven hours.<sup>4,5</sup> Its subsequent life in the tissues is difficult to ascertain precisely, but is almost certainly short—probably no more than a day or two.

Our knowledge of monocytes, derived mainly from studies of laboratory animals, suggests several differences from the neutrophil model. Monocytes also are produced from rapidly dividing marrow precursors and enter the circulation quite promptly after final cell division. However, once in the circulation, they persist in the blood for a longer time than do neutrophils; the half-time of circulating mouse monocytes has been estimated at 22 hours.<sup>7</sup> From the circulation, monocytes enter various tissues where some may differentiate into larger phagocytic cells (macrophages or histiocytes) that may survive for several months.<sup>8</sup>

From the Cancer Research Institute and Department of Medicine, School of Medicine, University of California, San Francisco.

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TABLE 1.—*Disordered Phagocyte Function—General Pathophysiology*

Defective Stage	Illustrative Clinical Disorders
Production of phagocytes	Agranulocytosis, acute leukemia
Migration to sites of inflammation	Neoplasia, steroid-treated patients
Chemotaxis	Hereditary disorders of complement function
Opsonization of microorganisms	Sickle-cell anemia, hypogammaglobulinemia
Killing of ingested microorganisms	Chronic granulomatous disease, hereditary myeloperoxidase deficiency.

Unlike the short-lived neutrophil which enters the circulation equipped with its maximal supply of bactericidal and bacteriolytic components, mononuclear phagocytes may adaptively increase their microbicidal effectiveness after reaching tissue sites.<sup>9,10</sup>

### Migration and Chemotaxis

The first facet of the phagocytic process to be considered is that of local accumulation of large numbers of these cells in areas of tissue damage or microbial invasion. Two test systems, the "skin-window" technique of Re buck and Crowley<sup>11</sup> and the chemotaxis chambers of Boyden,<sup>12</sup> have provided considerable information about this aspect of phagocytic function.

A "skin-window" is made by placing a coverslip over a superficially abraded area of skin.<sup>11</sup> Leukocytes that migrate to this area can be examined by periodic removal and staining of the coverslips or, in some modifications, by emptying a small collecting chamber. In normal adults, the cells observed after two to four hours are almost exclusively neutrophils. By eight hours, one-third to one-half of the cells adherent to coverslips are mononuclear phagocytes and at 24 hours mononuclear phagocytes predominate. Studies in animals suggest that these mononuclear phagocytes are derived from blood monocytes.<sup>8</sup>

Drugs and some disease states can impair the ability of neutrophils or monocytes to respond in this test. Decreased migration of neutrophils has been reported after the administration of steroids<sup>13</sup> and ethanol<sup>14</sup> to physically normal subjects. Patients with acute leukemia<sup>15</sup> or diabetes mellitus and ketoacidosis<sup>14,16</sup> also have impaired migration of neutrophils.

Diminished mononuclear cell response has been reported in untreated patients with advanced neoplasms and in patients receiving certain cytotoxic drugs to treat both neoplastic and non-neoplastic

disorders.<sup>17-19</sup> If these abnormal neutrophil and monocyte responses also occur in areas of microbial challenge, they could serve to provide the invading organisms with a critical head start in causing disease.

The term *chemotaxis* refers to the directional motion of a cell toward a substance in its environment. Certain bacteria have been shown to be chemotactic for neutrophils,<sup>20</sup> and antigen-antibody complexes also generate chemotactic substances when added to fresh serum.<sup>12</sup> Many contemporary studies of chemotaxis *in vitro* utilize a chamber, devised by Boyden, that contains two adjacent compartments separated by a Millipore filter that has pores just large enough to permit a leukocyte to wriggle through.<sup>12</sup> If a suspension of leukocytes is placed in one compartment and the test substance in the other, the number of leukocytes that migrate through the filter may provide a measure of the substance's chemotactic activity. Keller and Sorkin have analyzed some of the recent work on such chemotactic mediators.<sup>21</sup>

Ward and his associates have described several mediators of chemotaxis that are generated in rabbit or guinea pig serum by reactions involving components of complement. One, a trimolecular complex composed of the fifth, sixth and seventh components of complement, is generated after the addition to serum of antigen-antibody precipitates.<sup>22</sup> Other chemotactic factors of lower molecular weight are generated as a result of the cleavage of C3\* by plasmin<sup>23</sup> or of C5 by trypsin.<sup>24</sup> Additional factors, generated from serum or present in lysates of neutrophils, may exert chemotactic effects that are specific for certain macrophage populations.<sup>25</sup> Recently, it has been reported that sera from patients with deficiencies of C3 or C5 have impaired ability to generate chemotactic stimuli *in vitro* (Table 1).<sup>26,27</sup>

\*C3 and C5 are symbols for the third and fifth components of complement.

## Opsonization

Although certain bacteria may be ingested by leukocytes in the absence of serum, phagocytosis of many potential pathogens requires, or is facilitated by, the action of serum factors called opsonins.<sup>28</sup> By specific attachment or nonspecific adsorption to the bacterial surface, opsonins modify microorganisms so that they are readily ingested by leukocytes.

## Antibodies

Although early workers concentrated on heat-labile serum opsonins, opsonizing properties have been detected in several moieties of serum. The opsonizing activity of specific antibodies, arising from previous vaccination or natural infection with the challenging organism or with one sharing some of its antigenic determinants, is of prime importance for phagocyte function. The repeated infections incurred by patients with hypogammaglobulinemia result in large part from their deficiencies of such heat-stable opsonins and are ameliorated by replacement therapy with gamma globulin. Recent studies suggest that the capability of immune IgG to combine with a specific microorganism depends on the Fab portion of the antibody molecule, whereas its ability to act as an opsonin depends on its Fc portion.<sup>29</sup> The opsonic ability may be related to the presence of Fc-attachment sites on the cell surface of certain phagocytes.<sup>30</sup>

## Complement Factors

Since the early studies of Wright and Douglas,<sup>31</sup> it has been recognized that the phagocytosis of certain microorganisms is enhanced by heat-labile substances in the serum.<sup>32</sup> The studies of Hirsch and Strauss suggested that heat-labile opsonins were distinct from antibodies and from the complete series of complement factors causing immune hemolysis.<sup>28</sup> Recent investigations by Wood and his collaborators have provided evidence that certain complement factors, specifically the third and fifth components, are involved in the phagocytosis of pneumococci by leukocytes suspended in rat serum.<sup>33,34</sup> Binding sites for complement components have been detected on the surfaces of neutrophils and macrophages<sup>35</sup> and, in mononuclear phagocytes, these sites may show specificity for C3.<sup>36</sup>

## Complement Deficiencies in Man

Deficiencies of C3 or C5 may be associated with an increased susceptibility to bacterial infection in man.<sup>26,27</sup> Alper et al studied a young adult with Klinefelter's syndrome and a lifelong history of infections by various bacteria.<sup>26</sup> The concentration of C3 ( $\beta_{1c}$  globulin) in his serum was less than one-third of normal and, of that, most was present in an inactive form. *In vitro*, his serum had decreased hemolytic complement activity and exerted poor bactericidal power against certain Gram-negative organisms. It failed to support optimal phagocytosis of pneumococci or to generate normal amounts of chemotactic activity. These serum deficiencies could be corrected *in vitro* by addition of small amounts of normal serum, but not by addition of purified C3. It was suggested that the patient might lack a serum factor, as yet uncharacterized, required for normal stability and function of C3.

Miller and Nilsson described an infant with severe eczematoid dermatitis who experienced repeated cutaneous and systemic infections caused by *Staphylococcus aureus* and various Gram-negative bacteria.<sup>27</sup> Sera from the patient, her mother and numerous relatives were markedly deficient in their ability to generate chemotactic activity or to promote ingestion of yeast particles by leukocytes. The defective function could be corrected *in vitro* by normal sera or purified C5, but not by (rat) sera deficient in C5. Attribution of this patient's infectious diathesis solely to the deficiency of C5 is tempered somewhat by the lack of reported infections in numerous other similarly affected relatives.

## Other Opsonin Deficiencies in Man

From an historical standpoint it is instructive to recall that in 1904 Wright and Douglas noted that the incubation of human blood with viper venom reduced its opsonic activity, and they suggested that this could explain "the reduced resistance to septic infection which supervenes upon viper bites."<sup>31</sup> More recently, the sera of patients with sickle cell anemia have been reported to have diminished amounts of heat-labile opsonins for Type 25 pneumococci,<sup>37</sup> and it has been suggested that this deficiency, in conjunction with the functional asplenia of such individuals,<sup>38</sup> may underlie the unique susceptibility of these patients to pneumococcal sepsis and meningitis.



## Phagocytosis

The term *phagocytosis* refers to events associated with the envelopment and subsequent disposition of particles by certain cells. It is useful to consider the phagocytosis of microorganisms by leukocytes as composed of three sequential phases: (1) ingestion, the incorporation of extracellular organisms into cytoplasmic vacuoles; (2) the killing or inactivation of the ingested organisms; and (3) the digestion of killed organisms.

### Metabolic Events

Contemporary biochemical and metabolic analyses of the phagocytic process are based on the contributions of Karnovsky, Quastel and their colleagues.<sup>39,40</sup> Neutrophils derive the energy required for particle ingestion from glycolysis;<sup>41</sup> therefore, inhibitors of oxidative metabolism (cyanide, dinitrophenol, oxygen-free atmosphere) do not block particle uptake *in vitro* by these cells. In contrast, killing of ingested organisms is greatly impaired under anaerobic conditions.<sup>42</sup> The metabolic changes that follow particle ingestion by neutrophils include increased rates of lactate production, phospholipid turnover and ribonucleic acid (RNA) synthesis.<sup>39,40</sup> Most importantly in relation to neutrophil microbicidal activity, phagocytosis triggers a burst of oxygen consumption associated with greatly increased oxidation of glucose via the hexose monophosphate shunt; this reaction results in the intracellular generation of hydrogen peroxide.<sup>40</sup>

### Morphologic Events

During phagocytosis, cytoplasmic granules of leukocytes enter and release their contents into the phagocytic vacuoles containing ingested organisms.<sup>43</sup> Recent studies of rabbit "neutrophils" indicate that these granules are heterogeneous; subpopulations of intact granules have differences in their enzymatic constituents.<sup>44-46</sup> Substances detected in neutrophil granules from various mammalian species include numerous acid hydrolases, alkaline phosphatase, peroxidase, and a group of cationic proteins.<sup>47,48</sup> How are the various granule proteins related to the ability of leukocytes to kill and digest engulfed organisms?

Proteins with antibacterial activity have been extracted from the neutrophils of certain mammalian species. Important contributions to this research were made by Hirsch.<sup>49</sup> More recently

this approach has been pursued vigorously by Zeya and Spitznagel,<sup>48,50,51</sup> who have isolated and partially purified a group of cationic proteins from the granules of rat and guinea pig neutrophils and have demonstrated that these substances kill various bacteria *in vitro*. After fractionation, they found that the proteins differed in their amino-acid composition and in their ability to kill various species of bacteria.<sup>48,50</sup> More recently these authors have assigned the granule-associated cationic proteins to a specific subpopulation of neutrophil granules, which also exhibits eosinophilic staining characteristics.<sup>51</sup> It is not known whether similar cationic proteins are present in human neutrophils. Earlier attempts by these investigators to detect bactericidal cationic proteins in human granulocytes antedated techniques for obtaining pure monospecific cell populations, and the cationic proteins they detected in extracts of human leukocytes could have come from inadvertent contamination by eosinophils.<sup>52</sup>

What role is played by the enzymes contained in neutrophil granules? Some neutrophil granules are lysosomes—that is, they contain acid phosphatase and other hydrolytic enzymes with acid pH optima in an inactive, structurally latent form.<sup>47</sup> When the granule contents are released into phagocytic vacuoles, the enzymes become active and can participate in the degradation of bacterial macromolecules.<sup>53,54</sup> Muramidase (lysozyme) is also a component of neutrophil granules and acts to cleave the chemical bond linking two of the molecular constituents of bacterial cell walls. A few Gram-positive organisms, whose cell walls are stabilized principally by susceptible bonds, can be completely lysed by muramidase. However, like the other hydrolases, its major function is presumed to be the enzymatic digestion of organisms killed by other components of the leukocyte rather than primary bactericidal activity.

### Defects in Microbicidal Activity

Two recently appreciated "experiments of nature," chronic granulomatous disease and hereditary myeloperoxidase deficiency, have provided insights into molecular mechanisms employed by normal human leukocytes to kill bacteria and fungi (Table 2). Chronic granulomatous disease (CGD) was originally described as a familial disorder with X-linked inheritance, affecting only male children.<sup>55</sup> However, cases affecting females, with alternate modes of hereditary transmission,

TABLE 2.—Comparison of Two Hereditary Disorders of Leukocyte Function

	Chronic Granulomatous Disease	Myeloperoxidase Deficiency
Symptoms	Repeated infections, especially by staphylococci and organisms of limited intrinsic pathogenicity	Increased susceptibility to opportunistic mycoses ( <i>Candida</i> , <i>Aspergillus</i> ), but compatible with good health
Age at onset of infections	Infancy, childhood	May be delayed until adulthood
Sex incidence	Males predominate	Probably equal (few cases)
Genetic pattern	X-Linked inheritance (most male patients), other patterns (affected females and sporadic male cases)	Autosomal recessive inheritance
Cellular defect	Impaired $H_2O_2$ production (specific underlying defects may vary)	Impaired $H_2O_2$ utilization due to absence of myeloperoxidase
Clinical variants	With associated immunologic defects Job's syndrome Leukocyte glucose-6-phosphate dehydrogenase deficiency	Mosaic myeloperoxidase deficiency —with refractory megaloblastic anemia —with acute leukemia
Diagnostic leukocyte studies	Familial lipochrome histiocytosis NBT test Microbicidal assay	Peroxidase stain of blood smear Candidacidal assay

have recently been recorded.<sup>56-58</sup> CGD is manifested by a great susceptibility to severe infections which are often caused by microorganisms of limited intrinsic virulence.<sup>59,60</sup> Symptoms generally develop during the first two years of life, often in infancy. Lymphadenopathy with suppurative adenitis, repeated pneumonias, hepatosplenomegaly and skin infections are characteristic, and other sequelae may include rhinitis, conjunctivitis, osteomyelitis, meningitis and septicemia.<sup>60,61</sup> Eighteen of the 28 affected boys whose histories were reviewed by Johnston and McMurry died before their seventh birthday.<sup>61</sup> Although staphylococci and various coliform bacilli are the predominant causes of infection in these children, resistance to actinomycetes and certain fungi, especially *Candida* species, is also impaired.<sup>60,61</sup> Routine laboratory studies usually reveal anemia, leukocytosis, an accelerated sedimentation rate and hypergammaglobulinemia.

Quie and associates established a basis for the impaired resistance of affected children by demonstrating that leukocytes from CGD patients, although normally phagocytic, were deficient in bactericidal activity.<sup>62</sup> CGD leukocytes have a remarkable metabolic defect as well—they fail to develop the burst of oxidative metabolism and hydrogen peroxide generation that follows ingestion of particles by normal leukocytes<sup>63</sup> (Chart 1).

Several lines of evidence suggest that this metabolic deficiency is the cause of the bactericidal

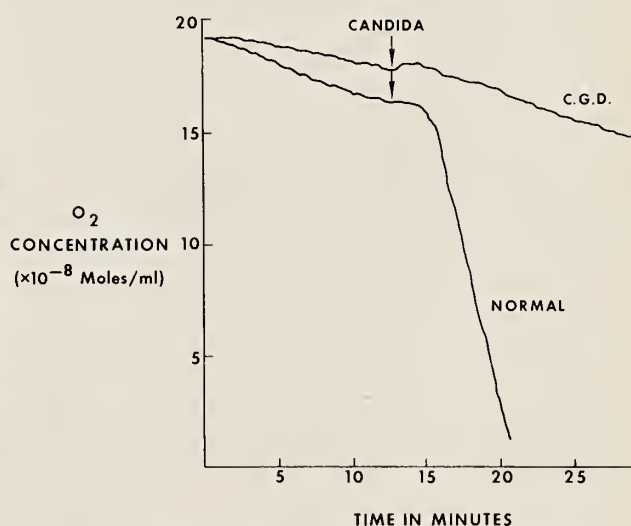
EFFECT OF PHAGOCYTOSIS ON  $O_2$  CONSUMPTION BY NORMAL AND C.G.D. LEUKOCYTES

Chart 1.—Different rates of oxygen consumption by normal and CGD leukocytes ( $1 \times 10^7$  neutrophils per ml) after they have phagocytosed heat-killed *Candida albicans* cells ( $3 \times 10^7$  per ml). The recordings, made with a Gilson model KM oxygraph with a Clark electrode (Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio) show the concentration of oxygen remaining in solution.

defect. The bactericidal and fungicidal activity of CGD leukocytes *in vitro* can be improved by providing an exogenous source of hydrogen peroxide<sup>64</sup> or by stimulating endogenous oxidative metabolism with redox dyes.<sup>65</sup> Moreover, CGD leukocytes kill certain hydrogen peroxide-producing bacteria (streptococci, lactobacilli and



pneumococci) relatively effectively, presumably because the bacteria supply the ingredient missing from these cells.<sup>66,67</sup>

At present, the diagnosis of CGD requires two observations: that the patient's leukocytes display deficient oxidative metabolism after particle ingestion, and that they exert defective microbicidal activity. The metabolic response to phagocytosis can be measured in several ways. Some, such as the method illustrated in Chart 1, are relatively direct but require special equipment that may not be readily available. Consequently, many investigators have favored the use of some variant of the nitro blue tetrazolium (NBT) test, which utilizes the fact that, after ingestion of particles in the presence of the essentially colorless NBT, normal leukocytes reduce it to an insoluble blue substance that accumulates in the cytoplasm. Although CGD leukocytes ingest particles normally, little of the NBT is reduced and consequently little blue color is formed.<sup>57</sup> The extent of NBT reduction can be measured spectrophotometrically after appropriate chemical extraction;<sup>57</sup> alternatively, the proportion of phagocytic cells containing the reduced NBT can be established by microscopic examination.<sup>68,69</sup>

Microbicidal activity is most often measured by some modification of the *in vitro* assay of Maale<sup>70</sup> as adapted by Hirsch and Strauss.<sup>28</sup> Known numbers of bacteria and leukocytes are combined under standardized conditions and serial colony counts are done on samples of the mixtures to record the rate of decline in viable bacteria. More recently described methods of determining leukocyte candidacidal activity may provide a somewhat simpler way to establish the presence of a microbicidal defect in leukocytes from children suspected of having CGD.<sup>71,72</sup> Although the standard tests of microbicidal activity measure neutrophil function, monocytes from the peripheral blood of CGD patients also exert impaired bactericidal<sup>73,74</sup> and candidacidal activity.<sup>75</sup>

The demonstration of disordered leukocyte function has provided for the more precise diagnosis of CGD; it also has resulted in expanding our clinical picture of the disorder. Cases fulfilling the criteria for CGD have been reported in girls<sup>56-58</sup> and diagnosed in children in their late teens.<sup>76</sup> The leukocyte defects of CGD have also been reported in association with other abnor-

malities, such as impaired leukotaxis<sup>77</sup> and selective immunoglobulin deficiency.<sup>78</sup>

A variant of CGD, manifested by recurrent cold staphylococcal abscesses from birth and occurring in fair-skinned, red-haired girls, was described by Davis, Schaller and Wedgwood, who named the condition Job's syndrome.<sup>79</sup> Bannatyne et al demonstrated defective NBT reduction and impaired bactericidal activity against staphylococci by leukocytes from a child with this disorder. Like leukocytes from male children with CGD, her leukocytes killed streptococci normally.<sup>68</sup>

In contrast, normal leukocyte bactericidal activity has been reported in studies of patients or animals with the Chediak-Higashi syndrome,<sup>80,81</sup> who also have frequent severe infections starting in infancy or childhood. This inherited abnormality is associated with oculocutaneous hypopigmentation and may terminate with the development of an atypical lymphoma.<sup>82,83</sup> Large cytoplasmic granules are present in various cell lines of affected patients, and the disorder may be diagnosed by finding the characteristic giant granules in leukocytes on conventionally stained blood smears.

Eventually, it should prove possible to classify CGD syndromes on the basis of their specific metabolic (enzymatic?) defects. Unfortunately, the studies designed to elucidate the mechanism that triggers the normal burst of postphagocytic oxidative metabolism and to discern the reason for its failure in CGD have produced a wealth of often conflicting information. Although detailed consideration of these studies is beyond the scope of this review, there are indications that CGD may be the expression of more than one specific cellular defect. Several recent papers can launch the interested reader into this interesting but controversial area.<sup>63,84-86</sup>

If defective production of hydrogen peroxide underlies the CGD syndrome (or syndromes), it is reasonable to consider how  $H_2O_2$  achieves its bactericidal activity. Klebanoff's studies indicate that the effectiveness of  $H_2O_2$  as an antimicrobial agent may be considerably augmented by its combination with a peroxidase. In a series of *in vitro* experiments with peroxidase enzymes derived from saliva, milk and leukocytes, he has shown that effective antimicrobial activity results from and requires the interaction of the peroxidase enzyme with  $H_2O_2$  and an appropri-

ate halide cofactor.<sup>67,87,88</sup> In his studies with  $H_2O_2$ , iodide and myeloperoxidase (MPO), the peroxidase of neutrophils and monocytes, bactericidal activity was associated with iodination of the bacteria.<sup>87</sup> Iodination of intracellular bacteria was demonstrated if normal leukocytes ingested microorganisms in the presence of low concentrations of extracellular iodide.<sup>67,87</sup> The extent of iodination was much diminished within CGD leukocytes, but could be demonstrated when viable,  $H_2O_2$ -generating organisms (lactobacilli) were ingested.<sup>67</sup> These observations, and studies by Sbarra and his associates,<sup>89</sup> strongly implicated MPO in the microbicidal activity of normal mammalian leukocytes.

The detection of hereditary myeloperoxidase deficiency, a syndrome characterized by the complete absence of peroxidase activity in neutrophils and monocytes, has permitted extensive evaluation of the role of MPO in the microbicidal affairs of human leukocytes.<sup>90,91</sup>

Hereditary MPO deficiency is readily diagnosed by examination of a peroxidase-stained smear of peripheral blood. In contrast to the characteristic deposition of dark reaction product on the cytoplasmic granules of normal neutrophils, monocytes and eosinophils (Figure 1), only the eosinophils of affected patients show peroxidase activity (Figure 2). The persistence of eosinophil peroxidase in this condition is in accordance with other observations indicating that the eosinophil enzyme is structurally and chemically distinct from MPO.<sup>92</sup> Thus far, five patients with hereditary MPO deficiency have been reported, including two pairs of siblings.<sup>90,93,94</sup> Its true incidence is unknown, and its apparent rarity may only reflect the paucity of attempts to detect it. Indeed, the first three reported subjects were discovered essentially by chance.<sup>93,94</sup>

In addition to the hereditary form of MPO deficiency, there have been reports of presumably acquired forms of the disorder; these forms are characterized by an enzymatic mosaicism of the peripheral blood neutrophils. In such patients, peroxidase-containing and peroxidase-deficient lines of cells coexist in the bone marrow and peripheral blood,<sup>95,96</sup> and additional hematologic abnormalities may be present. We have recently observed such a patient. Almost all of his neutrophils lacked peroxidase, and he died as a result of systemic fungal infection.

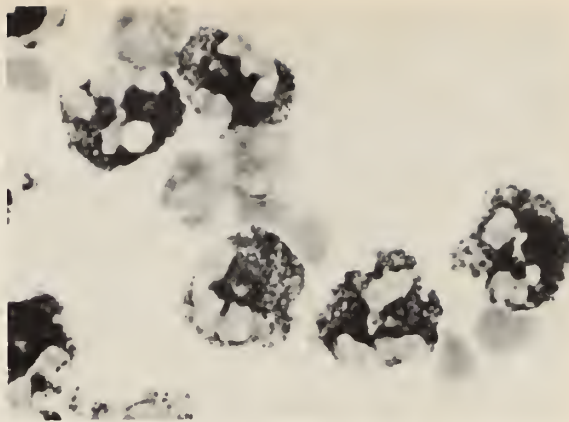


Figure 1.—Normal neutrophils, stained for peroxidase and counterstained with Giemsa. The peroxidase-containing granules are stained black and fill the cytoplasm of the cells. Original magnification X1250.

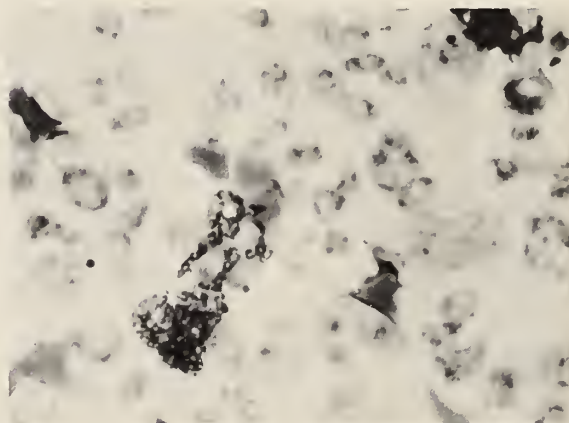


Figure 2.—Peroxidase stain of peripheral blood leukocytes from a patient with hereditary MPO deficiency. An eosinophil contains granules that are outlined by the peroxidase reagent. Neutrophils and monocytes all lack peroxidase activity. Original magnification X1000.

We have studied the leukocytes of three MPO-deficient subjects: a brother and sister with hereditary MPO deficiency, and a man with mosaic MPO deficiency in whom more than 99 percent of the circulating neutrophils were peroxidase-deficient. Peroxidase-deficient neutrophils were found to have an impaired ability to kill certain bacterial species. For example, the neutrophils of a patient with hereditary MPO deficiency required three to four hours to kill *Staphylococcus aureus* 502A or *Serratia marcescens* to the extent achieved by normal neutrophils in 45 minutes.<sup>91</sup> Curiously, as with CGD cells, the ability of MPO-deficient neutrophils to kill *Streptococcus fecalis* is relatively intact,



suggesting that this organism normally may be killed by an MPO-independent microbicidal mechanism.

Our patient with hereditary MPO deficiency was diagnosed after admission to the hospital with a systemic *Candida albicans* infection. In studies made over a period of years, his neutrophils have had a profoundly depressed ability to kill that organism<sup>72,90</sup> and certain other *Candida* species. In contrast, a strain of *Candida tropicalis* could be killed, although at a subnormal rate.<sup>97</sup> The patient's MPO-deficient monocytes also have had a greatly impaired ability to kill ingested *Candida albicans*.<sup>75</sup> The patient's sister has MPO-deficient neutrophils and monocytes and equally defective leukocyte candidacidal activity *in vitro*; she has, however, always been in good health and has remained free of infection. Likewise, the first three cases of hereditary MPO deficiency were detected in otherwise healthy adults.<sup>93,94</sup>

Thus, of the six persons with MPO deficiency either reported in the literature or known to us fully at this time, four have been otherwise healthy adults and two have had serious systemic mycoses. This may signify that MPO plays a special role in the antifungal defense mechanisms of normal man.<sup>98</sup>

Although MPO may increase the ability of neutrophils to kill a variety of bacteria,<sup>90,91</sup> the lack of clinically significant bacterial infection in many MPO-deficient individuals suggests that the residual leukocytic bactericidal activity can, in most circumstances, compensate for the lack of MPO. Comparison of the severity of the clinical manifestations of CGD, presumably caused by a deficiency in  $H_2O_2$  production, with that of hereditary MPO deficiency suggests that  $H_2O_2$  may activate leukocyte components other than MPO to produce bactericidal activity.

An attempt has been made to survey a rapidly expanding area of medical research. As the patterns of infectious disease in our hospitals have gradually changed under the influences of medical and socioeconomic factors, infections in "impaired hosts" have assumed greater importance. Studies such as those surveyed here not only increase our knowledge of factors that govern susceptibility or resistance to infection, but may eventually enable physicians to cope more successfully with the increasing challenge of opportunistic infections.

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# Specialty Conference

## Liver Conference

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ALLAN REDEKER, M.D., IRWIN SCHWEITZER, M.D., AND  
ROBERT PETERS, M.D.

*Taken from the weekly Liver Conference at the Los Angeles  
County-University of Southern California Medical Center,  
November 30, 1970*

DR. GOLDSTEIN:\* A four-year-old white girl was first seen in our Pediatric Admitting Room 18 April 1970 because of fever, vomiting, light colored stools and jaundice of two to three days' duration. Laboratory tests were ordered and she was sent home with a diagnosis of probable viral hepatitis. Symptoms of acute illness subsided but jaundice remained. She was brought back to LAC-USCMC 20 April 1970 because of a severe nosebleed and was admitted to the hospital.

Past history was negative except for occasional nosebleeds over a two-year period. The family doctor had detected anemia during a routine check-up one month previously, and had prescribed an iron-B complex liquid preparation. Jaundice had not been noted previously. She had had no blood transfusions and no injections except for immunizations during her first year.

Physical examination on April 20 showed moderate jaundice and lethargy. Vital signs were: temperature 99.6° F, pulse rate 140 and respiratory rate 20 per minute. Kayser-Fleischer rings were not seen. The liver edge was firmer than normal, moderately tender and extended 5 cm below the right costal margin on inspiration. The

spleen was not palpable. Neurological examination was within normal limits. Laboratory test results are shown in Table 1.

The child remained in the hospital for four days. Epistaxis ceased and she seemed more active and generally improved. Thereafter, at home, she appeared to be well, though with continued jaundice, until the onset of lethargy, vomiting, increasing jaundice, recurrent epistaxis and abdominal swelling during the first week of May. She was again admitted to hospital 9 May 1970 with jaundice and lethargy. A firm liver edge was palpable 8 cm below the right costal margin on inspiration and the splenic tip was palpable. There was mild pitting ankle edema and questionable shifting dullness in the abdomen. The patient remained in the hospital for ten days with gradual clinical improvement and some decrease in icterus. Shifting abdominal dullness disappeared and it was uncertain whether or not she did have ascites. A needle biopsy specimen of the liver was taken on the sixth hospital day, after improvement in the prothrombin time. In addition to the test results shown in Table 1, the hepatitis-associated antigen (HAA) test was positive, serum cerulo-

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No reprints available.

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TABLE 1.—Laboratory Tests on Propositus Patient

Date	4/18/70	4/23/70	5/9/70	5/19/70	7/1/70	9/23/70	11/25/70
Hb (gm per 100 ml).....	9.7		10.1		12.0		
WBC (mm <sup>3</sup> ) .....	3200		8400		8800		
Bilirubin, total/direct (mg per 100 ml).....	6.4/2.2	8.0/4.0	13.2/5.5	3.3/1.7	0.8/0.2	0.7/0.1	0.7/0.2
scOT (Karmen units/ml) .....	> 4000		3960	184	136	150	215
scPT (Karmen units/ml) .....	2840	750	1040	82	101		340
Alkaline phosphatase (B-L units per ml).....	10		8	6	12		
Albumin/globulin (gm per 100 ml).....		2.7/2.2	3.1/2.8	3.8/3.3	4.3/4.1	4.5/4.2	4.9/4.5
Prothrombin (percent) .....	< 5	59	32	100	100		
HAA .....	+		+		+		+

plasmin was normal, the Coombs test and the lupus erythematosus (LE) cell test were negative.

When the positive HAA test was obtained, a more detailed epidemiologic history was taken. The father had had hepatitis in 1967 and had been in hospital for one week. He admitted to occasional use of heroin intravenously and sometimes shared needles with friends. The mother had been admitted to a local hospital in 1968 with right upper quadrant pain and mild jaundice two weeks after delivery of her second child. At operation the gallbladder was gangrenous and cholecystectomy was performed. She received four blood transfusions during her stay in hospital. When tests were done on the father in July 1970, he was found to have a positive test for HAA, serum glutamic oxalic transaminase (scOT) of 77 and glutamic pyruvic transaminase (scPT) of 89 Karmen units per ml. The mother's serum was negative for HAA. A two-year-old sister of the patient had apparently been well with no episodes of jaundice but she had a positive test for HAA. scOT was 77 and scPT 103 units per ml, bilirubin was 0.8 mg per 100 ml and albumin was 4.4 and globulin was 3.2 gm per 100 ml. The paternal grandmother, who lives with the family, had been admitted to hospital in October 1970 with anorexia, fatigue and jaundice. Clinical and laboratory findings were typical for viral hepatitis. There was no history of injections or transfusions. The test for HAA was positive. She recovered satisfactorily in four weeks but the test for HAA remained positive in November 1970 and the scOT remained elevated at 200 units per ml. In November 1970, the propositus, the younger sister and the father continued to have a positive test for HAA.

The patient remains clinically well but the liver and spleen are still palpable and transaminase levels are still elevated.

## Discussion

DR. REYNOLDS:† It is now more than seven months since acute hepatitis developed in our patient and there are continued signs of activity of the disease judging from the increased serum transaminase activity and the positive HAA test. Probably, therefore, she has chronic hepatitis rather than a slowly resolving acute disease.

"Chronic hepatitis" is a relatively recently recognized syndrome with a wide clinical spectrum and probably multiple causes. Terminology, understandably, is in a state of flux. To most of us, chronic hepatitis indicates a combination of chronic liver disease and active hepatic inflammation. In the last analysis, "activity" is usually synonymous with an elevated serum transaminase level. This is probably a more reliable indication of active hepatic inflammation than such clinical features as jaundice, fatigue, right upper quadrant pain and hepatic tenderness, though these are often present concomitantly. Since there is *some* increase in serum transaminase in nearly all types of chronic liver disease, it is important to decide what level will be used to denote "active" hepatic inflammation. Soloway and colleagues at the Mayo Clinic have used a tenfold increase as a requirement for inclusion in a therapeutic trial of chronic active hepatitis.<sup>1</sup> Others use lower values, such as 200 Karmen units per ml, or have no fixed criteria. Chronicity in chronic hepatitis is indicated by a history of more than six months' duration or is implied by findings such as unusual firmness of the liver, splenomegaly, ascites, numerous spider angiomas or lowered serum albumin with raised globulin.

Our current classification of chronic hepatitis (subject to change without notice) is as follows (also see Table 2):

†Telfer Reynolds, M.D., Professor of Medicine.



TABLE 2.—*Classification of Chronic Hepatitis Currently Used by the Liver Service at Los Angeles County University of Southern California Medical Center*

<i>Designation</i>	<i>Etiology</i>	<i>Clinical Characteristics</i>	<i>Pathology</i>	<i>Serology</i>
I. Unresolved hepatitis (chronic persistent hepatitis, transaminitis)	Virus (SH and ? IH)	Persisting and fluctuating transaminase abnormality following viral hepatitis, without jaundice or clinical or laboratory evidence of progression to cirrhosis.	No cirrhosis nor fibrosis Uniform cobblestone arrangement of liver cells Occasional focal hepatocytolysis	HAA positive in 25% SMA negative LE negative
II. Chronic active viral hepatitis	Virus (SH)	Progression from icteric or anicteric long-incubation period, HAA-positive hepatitis to liver cirrhosis. Continuous mild or phasic activity with transaminase increase and occasionally jaundice.	Fibrosis and regeneration, usually cirrhosis Focal necrosis, cellular exudate, Kupffer's cell hyperplasia	HAA positive SMA negative LE negative
III. Chronic active lupoid hepatitis (plasma-cell hepatitis)	Uncertain (? immunologic)	Insidious onset Phasic episodes of jaundice and/or high transaminase activity superimposed on a gradually progressive coarsely nodular cirrhosis. Most patients are women and one-third have extrahepatic lupoid manifestations.	"	HAA negative SMA usually positive LE positive
IV. Chronic active toxic hepatitis	Oxyphenisatin (? other toxins)	Chronic jaundice and high transaminase activity progressing to liver cirrhosis.	"	HAA negative SMA often positive LE occasionally positive
V. Chronic active (cryptogenic) hepatitis (active chronic hepatitis, chronic aggressive hepatitis)	Uncertain	Similar to category III except for the absence of extrahepatic "lupoid" manifestations.	"	HAA negative SMA often positive LE negative

## I. *Unresolved Viral Hepatitis*

During the past eight years, Dr. Redeker and Dr. Peters have collected a group of patients from the hepatitis follow-up clinic who appear to have recovered clinically but continue to have irregular elevation of serum transaminase activity.<sup>2</sup> Both SCOT and SCPT activities are increased to an approximately equal degree. Both may be perfectly normal for weeks at a time but more often than not they are abnormal, with values from two to as much as twenty times the upper limit of normal. The elevations are not accompanied by jaundice and usually bear no relationship to the generally benign clinical status of the patient. The liver is often palpable but does not become firm or greatly enlarged. The spleen is occasionally palpable but the clinical and laboratory features of liver cirrhosis have not yet developed in any of the patients, even after several years of observation. Other terms used for chronic hepatitis of this type are "transaminitis" and "chronic persistent hepatitis."<sup>3</sup> The ultimate fate of such patients is still uncertain.

## II. *Chronic Active Viral Hepatitis*

Following an episode of icteric or anicteric viral hepatitis, such patients either have continuous low grade activity of their liver disease or phasic episodes of activity with jaundice and moderate or marked transaminase rise. The SCOT is usually higher than the SCPT. The clinical features of hepatic cirrhosis appear rather rapidly. The test for hepatitis-associated antigen is intermittently or continuously positive. Of approximately 25 patients that we have seen with this type of hepatitis, one-third have been followed from an episode of acute hepatitis and the remainder presumably have had a sub-clinical onset.

We have seen two children with chronic progressive liver disease whose illness seems to have begun with a typical episode of acute viral hepatitis but who have had a persistently negative test for HAA. This may mean that short-incubation-period hepatitis can cause chronic liver disease but we are uncertain of this and will probably remain so until some marker is available for "infectious" hepatitis. In our experience, most HAA-negative chronic hepatitis patients whose illness was said to begin with acute hepatitis have turned out to have clear evidence of chronic disease (that is, reversed albumin:globulin ratio) when the rec-

ords of the acute illness were available for inspection.

## III. *Chronic Active Lupoid Hepatitis*

Patients in this category usually have chronic liver disease when first seen, implying that the initial illness was anicteric and possibly asymptomatic. In the very few patients in whom we have witnessed what may have been the initial illness, there were invariably features that were unusual for acute viral hepatitis (a protracted course, a positive LE cell test, rapid development of hyperglobulinemia or unusual numbers of plasma cells on liver biopsy). In lupoid hepatitis, there is usually phasic rather than continuous activity superimposed on a gradually evolving coarsely-nodular cirrhosis. Most patients are female and the age range is wide, from childhood to the sixth or seventh decade. By definition, the LE cell phenomenon is demonstrable at some stage of the illness. Non-hepatic manifestations such as arthritis, autoimmune hemolytic anemia, skin rash, fever, nephritis or ulcerative colitis are present in approximately one-third of this group, but the liver disease is always the dominant feature.

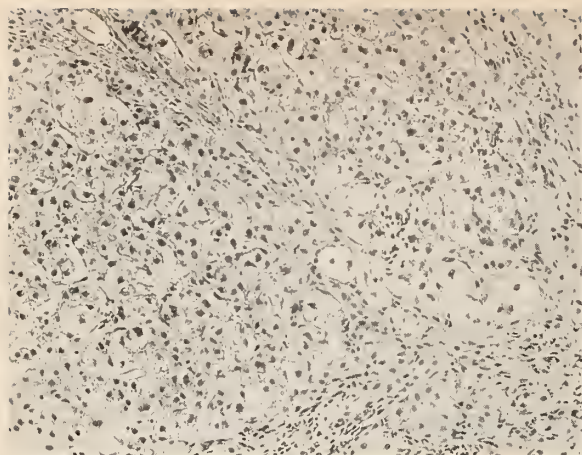
## IV. *Chronic Active Toxic Hepatitis*

We have been surprised to find recently that typical chronic active hepatitis can be caused by chronic or intermittent exposure to a laxative, oxyphenisatin. Long continued ingestion of this drug can cause either an acute viral hepatitis-like illness<sup>4</sup> or a more chronic liver disease with histologic and clinical features fitting the definition of chronic active hepatitis.<sup>5</sup> We know of two patients with chronic hepatitis and a positive LE cell test whose illness was probably caused by oxyphenisatin. This raises the disturbing possibility that other environmental toxins or drugs may cause chronic hepatitis.

## V. *Chronic Active Hepatitis*

If the test for HAA is negative, the LE cell phenomenon is not demonstrable, and there is no recognizable toxin operative, we place patients with chronic hepatitis in this "unspecified" category. From a clinical standpoint, these patients resemble those with lupoid hepatitis except that there are fewer extrahepatic manifestations. The female preponderance and the wide age range are similar and the onset is usually insidious.





**Figure 1.**—Photograph of the microscopic appearance of liver showing swollen liver parenchymal cells and strands of fibrous tissue extending diagonally across the photograph. There are a few small foci where liver cells are undergoing destruction right above the diagonal band of fibrosis (H&E X 140).

Our patient today clearly belongs in the second category of chronic hepatitis and raises some interesting epidemiologic questions.

Dr. Peters will describe the liver biopsy and tell us something about the pathology and serologic tests in the various types of chronic hepatitis.

DR. PETERS: \* The liver biopsy taken on May 19, 1970 (Figure 1) showed that the lobular architecture was completely distorted by regenerative nodules and thin fibrous septa. The liver cells were hydropic and numerous acinar structures and cobblestone-appearing arrangement of liver cells effaced the usual liver cord pattern. Within the poorly defined nodules were scattered foci of hepatocytolysis with lymphocytes and Kupffer cells filling the void left by the destroyed parenchymal cells. Kupffer cells, in general, were only slightly hyperplastic. There were occasional small canalicular bile plugs.

At one time we would have called this histologic lesion, chronic active hepatitis and would have considered it to be an autoimmune-related liver disorder.<sup>6</sup> The demonstration of HAA in the serum of this patient and other patients with similar hepatic morphologic changes has caused us to re-evaluate chronic liver disease and its relationship to viral hepatitis.

To review a great deal of work very briefly, most of you are familiar with the story of Dr. Blumberg's identification of the hepatitis-associ-

ated antigen in 1965. At that time, Blumberg was screening sera of different racial groups in a search for genetic differences in serum proteins. Using agar gel as a diffusion media and plasma from hypertransfused hemophiliacs as antisera, he encountered a reaction against the serum of an Australian aborigine.<sup>7</sup> Dr. Blumberg named this antigen the Australia antigen. Many investigators still use this term, although in 1969 a National Institutes of Health conference at Yale University agreed on the use of the term *hepatitis-associated antigen* (HAA). Subsequent to Dr. Blumberg's discovery, several investigators, including Dr. Blumberg, demonstrated the appearance of HAA in the sera early in the course of long-incubation-type of viral hepatitis, whether transmitted parenterally or nonparenterally, but not in short-incubation hepatitis (epidemic or infectious hepatitis).<sup>8-10</sup> Krugman and his associates, who had worked for many years at the Willowbrook State School with a short-incubation, hepatitis-producing agent that they call ms-1, and a long-incubation hepatitis-producing agent that they called ms-2,<sup>11</sup> found that patients in whom hepatitis developed after inoculation with the ms-2 agent always began to have serum HAA just before the rise of SGPT activity. Those in whom hepatitis developed after inoculation with the ms-1 agent, never had HAA in their sera.<sup>12</sup> This supported Krugman's long-held contention that ms-2 was similar to or identical with the serum hepatitis agent, whereas ms-1 was probably the agent for infectious hepatitis.

Electron microscopic studies of the serum from patients who have demonstrable HAA show both round and filamentous 20 millimicron diameter particles in large abundance which can be shown to clump with HAA antisera<sup>13,14</sup> and, in addition, sparse 45 millimicron particles<sup>15</sup> (Figure 2). Biochemical analysis of the purified antigenic substance has demonstrated such a low nucleic acid content<sup>16</sup> that it is generally believed that the bulk of the antigenic material is not infective virus. However, a transfusion or inoculation of material that contains HAA causes some manifestations of viral hepatitis in about 75 percent of recipients.<sup>17</sup> Thus the evidence is quite good that a demonstrable and immunologically characteristic substance has finally been found that is related to the agent of one type of viral hepatitis—apparently the long incubation type (so-called serum hepatitis or hepatitis B by the older terminology). Obviously this

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**Figure 2.**—Electron photomicrograph showing three types of particles commonly found in HAA positive sera. At the periphery (arrow) are the small 200 Å particles and in the center are the larger particles of 450 Å closely associated with a tubular segment (222,000 X).

marker constitutes a major advance in the study of viral hepatitis.

Now that a marker associated with acute long incubation viral hepatitis is fairly well established, we have the opportunity to study the fact and fiction of the maladies that have paraded under the term of chronic hepatitis.

### Unresolved Hepatitis

In following the sera and histologic pattern in liver of patients convalescing from viral hepatitis, it is found that about one fourth of patients with unresolved hepatitis continue to have strong titers of HAA in sera. The most prominent, although usually overlooked, histologic feature in the livers of such patients is the cobblestone arrangement of parenchymal cells, a result of the continued regenerative activity. The liver cells are uniformly swollen and pale with slightly enlarged nuclei, and only sparse foci of hepatocytolysis can be found. The Kupffer cells are not prominent. To date, none of the patients followed has completely recovered; serial liver biopsy shows the histologic pattern retained for as long as we have followed the patients—eight years in some instances. Cirrhosis has not developed in any of the patients.

Persons with unresolved hepatitis probably are the endemic pool for serum hepatitis. If we assume that a similar proportion of patients whose initial viral disease was subclinical will also have unresolved viral hepatitis, the potential hepatitis pool becomes frightfully large.

Those who have a high risk of parenteral or nonparenteral contact with hepatitis and a low

immunologic competence tend to acquire HAA with or without clinical disease and many continue to carry the antigen in their serum. Such patients include institutionalized children with Down's syndrome,<sup>13</sup> patients with lymphomatous disease who have received blood transfusions, patients on renal dialysis<sup>18</sup> and probably many other special groups. The incidence in the so-called normal population runs from less than 0.1 percent in parts of the United States to as high as 15.5 percent in Taiwan.<sup>19-21</sup> In the Los Angeles area, 0.3 percent of donors to the Red Cross have HAA positivity.<sup>20</sup>

### Chronic Active Hepatitis Syndromes

The histologic picture of chronic active hepatitis is one that shows chronicity with a superimposed cytologic and inflammatory pattern of hepatitis. Usually by the time the biopsy is taken, the liver is truly cirrhotic. However, livers of some patients in the early stage may have only hepatic fibrosis in portal areas and some regenerative activity. Usually the areas of fibrosis are heavily infiltrated by lymphocytes and often by plasma cells. The liver parenchymal cells are no longer arranged in a cord pattern, they are ballooned and the liver cell nuclei are large with crisp nuclear membranes. The parenchyma is involved to a varying extent by focal hepatocytolysis with lymphocytes, plasma cells and Kupffer cells occupying the small foci vacated by the destroyed liver cells. Although "piecemeal" necrosis has been emphasized as a characteristic change occurring in the periphery of the nodules or periportal areas, we have not found this to be a distinctive feature of chronic active hepatitis, which instead is better characterized by the evidence of continuing regeneration and focal necrosis of liver cells. In contrast to ordinary viral hepatitis, there does not seem to be the centrilobular or centronodular accentuation of the parenchymal cell hydropic swelling, and cytologic changes are more uniform across the entire lobule or nodule but one nodule may differ from its neighbor. At times when the serum transaminase activity is diminished or nearly normal, there is less destructive activity histologically, and occasionally the regenerative and necrotizing processes will be entirely quiescent.

In light of recent demonstration of HAA in sera of many patients with chronic liver disease, some investigators have assumed that all instances of



chronic active hepatitis are due to viral hepatitis. However, in the patients we have observed, those with chronic active lupoid hepatitis do not have HAA. In a large enough series, one might expect to find an incidence of HAA positivity in the sera of patients with lupoid hepatitis similar to that in the rest of the population.

Chronic active viral hepatitis is histologically indistinguishable from chronic active lupoid hepatitis. We use the term chronic active *viral* hepatitis when patients have HAA in sera, and the term chronic active *lupoid* hepatitis when the LE phenomenon is demonstrable. The patient presented today belongs to the former group, HAA-positive viral hepatitis having developed in infancy, with progression to cirrhosis.

A large group of chronic hepatitis patients have negative HAA and no LE phenomenon but do have smooth muscle antibody (SMA) or antinuclear antibodies in sera, suggesting some immunologic component to their disease. Some of us believe the patients with chronic active hepatitis and SMA in sera really have the same basic disease as those who show, in addition, a positive LE cell preparation.

There still remains a group of patients who have neither HAA nor any immunologic serum reaction, and we call their disease simply chronic active hepatitis. These patients with negative HAA, SMA and LE cell tests may not be a uniform group and may have any of several different causes for their progressive liver disease and necrosis. Their disease may be a sequela of short-incubation viral hepatitis or prolonged exposure to a toxin, or it may be chronic active viral hepatitis or chronic active lupoid hepatitis with serum factors too weak to demonstrate.

A recent finding has been the high incidence of HAA in sera of patients who have liver cell carcinoma. We have demonstrated HAA in nine of thirteen non-alcoholic cirrhotic patients with liver cell carcinoma, but not in any of the patients with liver cell carcinoma arising on a background of alcoholic cirrhosis. Tong *et al* have found that 80 percent of 55 patients from Taiwan with liver cell carcinoma have HAA.<sup>20</sup> In Uganda, 40 percent of patients with liver cell carcinoma have HAA in the serum.<sup>22</sup> On the other hand, we have not found serologic tests characteristic of chronic active lupoid hepatitis in patients with liver cell carcinoma either from the United States or from Taiwan. We have not observed progression to liver cell car-

cinoma in any patients with chronic active lupoid hepatitis. In the past, we have tended to believe that neoplasia was simply an end stage of the natural course of development of cirrhosis. However, a difference in incidence of carcinoma occurring in patients with chronic active viral hepatitis as contrasted with chronic active lupoid hepatitis raises the possibility that the viral agent itself may be oncogenic.

The identification of the hepatitis antigen is made by several techniques. In the initial demonstration, Blumberg used a modification of Ouchterlony double diffusion in agar gel in which the precipitation arc develops between the antiscrum and the serum containing the antigen. By use of a hexagonal pattern with a central well containing the antibody and the six peripheral wells containing four unknown and two antigen control sera, one can establish lines of identity in the precipitation arcs and also screen for antibody at the same time. The Ouchterlony technique remains the back-up method, but as originally described, it takes seven days to be certain that a specimen is negative, and only about 40 percent of patients with post-transfusion hepatitis have identifiable HAA even when SCPT activity is over 1000 Karmen units per ml.<sup>21</sup> The complement fixation technique was developed shortly after the importance of the antigen was recognized, and many laboratories feel that this is a highly sensitive method of detection. The development of automated complement fixation techniques that take only an hour offers some promise for mass screening if its sensitivity can be assured.

It was recognized by many investigators that the antigen moves during electrophoresis in the alpha-1 range and that the antibody, which is an IgG type, moves in the opposite direction. Therefore, during electrophoresis, antigen from the test serum moves toward the antibody in an opposing well. This technique, generally referred to as the immuno-electro-osmophoresis (IEOP), has stimulated a great deal of effort and many commercial kit type devices are now available on the market, some of them quite sensitive. The test can be performed at low or high voltage and takes between 35 minutes and two hours. Probably the most sensitive technique is the radio-immuno assay but the test time required and equipment necessary have kept this method in the research laboratory.

We found some time ago that a simple concentration of the test serum to tenfold its original

concentration by use of a polyacrilamide gel allowed us a better sensitivity with agar gel diffusion than the complement-fixation technique or the routine IEOP. We detected HAA in 83 percent of patients with post-transfusion hepatitis when SCPT activity was over 1000 units.<sup>21</sup> We still use this technique in our laboratory for establishing lines of identity of positive sera with control antigen. However, although 90 percent of the reactions are demonstrable in about 12 hours, some precipitation arcs still come up as late as six days. For screening of blood donors, this technique is obviously not satisfactory and we have found that the IEOP technique using tenfold concentrated sera gives us our best screening technique and highest sensitivity. We are hopeful that the recent development of a hemagglutination inhibition test with purified antigen attached to red cells will allow a simple, cheap, highly sensitive technique that will give rapid results.

DR. REDEKER: \* There seems little doubt that today's patient now has cirrhosis. Finding the HAA present is of interest, but not a surprise. One is impressed with how quickly the features of cirrhosis followed the episode of apparent acute viral hepatitis. From both of these standpoints, this case is entirely like all of the few instances we have observed of clear-cut acute hepatitis progressing to cirrhosis. First, all of our patients following this course have been acutely and chronically HAA positive. Among adults, we have not recognized the development of cirrhosis from an initially HAA-negative type of hepatitis. Second, the progression to cirrhosis has been one of a rapid transition from acute-phase hepatitis to cirrhosis, usually in less than a year. It may well be that "infectious viral hepatitis" (short-incubation hepatitis or IH) does not progress to cirrhosis but that only HAA-positive hepatitis (long-incubation or serum hepatitis) has this potential. Such a conclusion will have to await the availability of other "markers" for the identification of infection with the IH virus or viruses.

The most common long term sequela of viral hepatitis is "unresolved viral hepatitis." This lesion is rarely associated with recurrent jaundice but instead is characterized by persistent or recurrent elevations of SGOT and SCPT, abnormal bromsulphalein retention, essentially normal values for serum proteins and generally good health. This would appear to be the disorder affecting the two-

TABLE 3.—*Follow-up Studies (6 to 18 Months) of 134 Patients with Acute Hepatitis and a Positive Test for HAA*

	Number	HAA Positive
Biochemically normal . . . . .	121	1 (0.8%)
Unresolved hepatitis . . . . .	13	5 (38%)
Total. . . . .	134	6 (4.5%)

year-old sisters and the father of the patient. Each is HAA positive and presumably chronically so. Studies from our Hepatitis Unit show that in 9.7 percent of patients with acute HAA-positive hepatitis, "unresolved hepatitis" developed (Table 3). A significant fraction of these patients remain persistently HAA positive (approximately one-third). On the other hand, only 0.8 percent of the patients with complete biochemical resolution of their hepatitis show persistence of HAA. Over-all, 4.5 percent of initially HAA-positive patients remain so, no doubt becoming the endemic pool of carriers referred to by Dr. Peters.

The question that must then be posed is whether these persistently HAA-positive patients are contagious. Certainly the presence of HAA seems to identify blood products that are infectious when administered parenterally. Gocke and colleagues<sup>17</sup> have shown a striking relationship between HAA in donor blood and the subsequent development of post-transfusion hepatitis. Krugman and Giles<sup>23</sup> demonstrated the infectivity of HAA-positive serum injected intramuscularly. Probably more important in relation to the present case, these investigations also demonstrated infectivity of HAA-positive serum when fed orally. The incubation period was long, characteristic of the viral agent rather than the route of administration. Supporting this was the earlier observation of Mirick and Shank<sup>24</sup> of secondary cases of hepatitis among contacts of patients with post-inoculation serum hepatitis (long-incubation type). With the advent of HAA testing, most investigators were startled to recognize that, at least among adults, approximately 50 percent of all apparently non-parenteral hepatitis was HAA-positive, presumably, due to infections with the SH virus. We have observed a number of instances of acute hepatitis occurring among household contacts of persistently HAA-positive patients with no evidence for any parenteral contact. Thus, it appears that (a) serum positive for HAA is infectious and (b) HAA-positive patients are potentially infectious by some form of person-

\*Allan Redeker, M.D., Professor of Medicine.



to-person contact. It should be pointed out that direct challenge has only been done with serum per os, not feces. Fecal shedding of HAA has not yet been demonstrated, although, probably the stool could be periodically contaminated by HAA-positive blood.

Very likely the original patient with hepatitis in this family was the father, who has now become a hepatitis carrier. The younger sibling probably contracted hepatitis from the father and now is also a carrier. Either could have provided the source of infection for the *propositus* patient. The most recent instance of acute hepatitis in the grandmother further supports the concept that the carriers in this household are infectious.

The question of gamma globulin prophylaxis for HAA-positive hepatitis contacts must be raised. Unfortunately, there is no reason to believe that conventional gamma globulin provides any element of protection or modification for HAA-positive hepatitis. Krugman was unable to demonstrate any neutralization of the serum hepatitis agent when gamma globulin was mixed with SH-containing serum, then injected intramuscularly.<sup>23</sup> In a recent study of our own of hospital personnel who had been exposed to HAA-positive serum by an accidental needle stick, it was found that hepatitis developed in six of fifteen (40 percent) although each had received 20 ml of gamma globulin. Supporting these observations is the recent report of the National Cooperative Post-Transfusion Hepatitis Study showing no protection from hepatitis with 10 ml of gamma globulin given on three occasions after transfusion.<sup>25</sup> The virus associated with HAA may be of very low immunogenic potency, since it is rare to observe detectable antibody during recovery from hepatitis and since none has been detectable in standard gamma globulin preparations.

DR. REYNOLDS: With evidence of hepatitis in two young children, one could speculate about transplacental infection from the mother. Dr. Schweitzer, of our Hepatitis Unit, has collected some interesting data bearing on this possibility.

DR. SCHWEITZER: \* The hepatitis-associated antigen was studied in 44 mother-infant pairs. These pairs were made up of women in whom typical acute viral hepatitis developed during pregnancy or within six months of delivery and whose newborn were tested for HAA at least one time. The purpose of the study was to determine the fre-

quency of transmission of HAA or of viral hepatitis from mother to infant, to consider the possible mode of such transmission, and to study the course of this illness in newborn children. Our early results have been reported.<sup>26</sup>

Twenty mothers were HAA-positive during acute hepatitis, and seven of their babies were found to be HAA-positive. Seventeen women were HAA-negative while ill, and seven were not tested. None of their babies became HAA-positive.

There was a total of seven HAA-positive babies. One has been HAA-positive for more than 15 months without any sign of hepatitis. Another has been HAA-positive for more than 12 months with prolonged, subclinical hepatitis which has now apparently resolved. Two have remained HAA-positive for over five months without apparent hepatitis. One has been HAA-positive for over five months with prolonged sub-clinical hepatitis. Another was found to be HAA-positive at ten months of age and sub-clinical hepatitis has since developed. One has recently been found to be HAA-positive at seven weeks of age with no signs of hepatitis as yet.

All mothers of the HAA-positive babies were HAA-positive at the time of their acute hepatitis. In one the onset of the hepatitis was six weeks before delivery, in three the onset was at the time of delivery, and in three it was one month postpartum.

In ten cases cord blood was tested for HAA and all were found to be negative. In four cases the mothers were HAA-positive at delivery. The babies of two of these subsequently became HAA-positive and the babies of the other two remained HAA-negative. Six mothers were HAA-negative at delivery and none of their babies became HAA-positive.

The data demonstrate that the transmission of HAA from mother to infant is not uncommon (35 percent in our cases). The mode of transmission is less clear. Four of the cases suggest that HAA may not cross the placental barrier: The mothers' serum was HAA-positive at the time of delivery, the umbilical cord samples were HAA-negative, and two babies of these women subsequently became HAA-positive.

The hepatitis-associated antigen seems to remain in the serum of affected infants for long and perhaps indefinite periods. None of our HAA-positive infants have become HAA-negative and one has been followed for more than 15 months. When hepatitis develops in these infants it is sub-clinical

\* Irwin Schweitzer, M.D., Instructor in Medicine.

and detectable only by biochemical tests (for example, SGPT in a 700 to 1600 range). The course is several months and the end results remain unknown. One is fearful that hepatic cirrhosis secondary to chronic viral hepatitis may develop in some of these children.

DR. REYNOLDS: From what we have heard, we can conclude that the father is the probable source of infection in the family of today's patient and that the prognosis for her is limited, while the sibling and father may remain asymptomatic carriers indefinitely. Perhaps of more than passing interest is the fact that the four HAA carriers in this family are blood relatives, giving support to the theory of Blumberg and colleagues that a genetic trait is involved.<sup>19</sup>

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## MEDICAL STAFF CONFERENCE

# The Pathogenesis, Diagnosis, And Treatment of Pulmonary Embolus

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SLEISENGER:\* The use of anticoagulant drugs in pulmonary embolism is established, but pulmonary embolism continues to be one of the more serious and more important clinical conditions. Dr. Abdallah will present a case which illustrates some of the clinical problems associated with pulmonary embolism.

DR. ABDALLAH:† This was the sixteenth admission to this hospital of a 57-year-old Caucasian woman who had a long history of rheumatic heart disease, hypertension, coronary artery disease, gout and adult-onset diabetes mellitus. The chief complaints on admission were dyspnea and chest pain. Her present illness dated back to her first pregnancy, when she had an episode of thrombophlebitis. She was last in hospital here five months ago with severe congestive heart failure and vague chest pains. At that time diagnosis of pulmonary embolus was made mainly on the basis of changing lung scans. Anticoagulants were administered, and she was discharged after sodium warfarin (Coumadin®), digoxin and diuretic therapy was initiated. However, because of hemorrhagic complications the Coumadin was discontinued three months before the present hospital admission.

During the month before admission, the patient had increasing dyspnea, orthopnea, paroxysmal nocturnal dyspnea and a 25-pound gain in weight. Two days before admission she noted pleuritic left anterior chest pain and increasing dyspnea. The past medical history was significant in that in 1956 she had a transient right hemiparesis, and in 1957 a probable acute myocardial infarction. In 1957 she was found to have the murmurs of mitral stenosis and insufficiency and atrial fibrillation. In 1960 closed mitral commissurotomy was carried out. From 1961 to 1969 she had multiple hospital admissions, mainly for episodes of congestive heart failure. In 1969 right and left sided cardiac catheterization were compatible with primary left ventricular failure.

On physical examination the patient was sitting upright and was in obvious respiratory distress. Blood pressure was 170/90 mm of mercury, the pulse was irregular at 60 beats per minute and respirations were 22 per minute. The patient was afebrile. Grade II Keith Wagner retinopathy and jugular venous distension were noted. Examination of the chest revealed a prolonged expiratory phase with diffuse wheezes and scattered rales at the left base. Cardiac examination demonstrated cardiomegaly, murmurs of mitral stenosis and in-

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sufficiency, an opening snap, and a loud pulmonic second sound. The liver was tender and palpable 6 cm below the right costal margin. Peripheral edema and a tender right calf with a positive Homan's sign were also present. The remainder of the examination was within normal limits.

Pertinent laboratory data included a hematocrit of 38 volumes percent, a normal white blood cell count, sodium of 148 mEq, potassium of 2.7 mEq, chloride of 101 mEq and CO<sub>2</sub> of 30 mEq per liter, and creatinine of 1.3 mg per 100 ml. Serial transaminase determinations were within normal limits. An electrocardiogram showed atrial fibrillation, left ventricular hypertrophy, ST-T wave changes of ischemia and U waves. An x-ray film of the chest showed increased cardiomegaly and redistribution of blood flow to the upper lobes. The lung scan performed on the day after admission showed improvement of the left lateral defect present five months earlier. A clinical diagnosis of congestive heart failure and pulmonary embolus was made. Treatment, including heparin and diuretic administration, bed rest and salt restriction, was initiated. The patient showed gradual improvement and was discharged after three weeks.

DR. SLEISINGER: Thank you, Dr. Abdallah. We have asked Dr. Murray, Chief of the Chest Unit at San Francisco General Hospital, to discuss this patient. Dr. Murray has had long experience with this particular disease.

DR. MURRAY: \* Thank you Dr. Sleisenger. The subject of pulmonary embolism has been talked about extensively the past few years and is generally introduced with the remarks that it is widely known to be the most commonly missed major medical diagnosis and that it is an extremely common finding in routine autopsy in general hospitals. Pulmonary embolism has also been implicated as the major cause of death, or at least a major contributing cause of death, in such routine autopsies. In the autopsy series the incidence of observed pulmonary embolism certainly was much higher than the incidence of clinically diagnosed pulmonary embolism.<sup>1</sup> I will try to emphasize some of the more unusual manifestations of pulmonary embolism which should alert you to its possible presence, following which appropriate diagnostic procedures can be carried out and treatment begun. The incidence of pulmonary

embolism is very difficult to determine. Some authorities have speculated that some embolization is going on all the time, even in perfectly healthy persons. It is believed that aggregates of platelets and fibrin are filtered out as they pass through the lungs, but that these are few in number so that few vessels are blocked and the neuro-humoral consequences that accompany the arrival of large clots in the lungs are absent.

Clinically important pulmonary embolism begins with the formation of a thrombus somewhere in the peripheral venous system or in a vascular cavity. After the thrombus is formed numerous large fragments may be shed into the venous system and travel to the lungs. In the middle of the nineteenth century Virchow first identified the three factors that are thought responsible for the development of thrombosis: vascular damage, hypercoagulability of blood, and stasis of blood flow. Injury to the endothelium from trauma or operation is obviously an important contributing cause since the damaged site serves as the nidus for fibrin deposition and the formation of a thrombus. Hypercoagulable states of the blood also deserve mention, although they remain an enigma. They are often hard to detect in the laboratory, but have been documented clinically in disorders such as polycythemia rubra vera in which both the number of red blood cells and platelets are substantially increased. We now also believe that a number of drugs, particularly estrogens either alone or in combination in the birth control pill, can introduce a hypercoagulable state. Stasis very commonly accompanies the development of thrombosis and may result from bed rest, immobilization of an extremity, or from an incompetent venous system in the lower extremities. Stasis is not always associated with embolic disease even though clots form in peripheral vessels, as they can either be lysed *in situ* or can become densely adherent to the vessel wall. If a part breaks off, travels to the lungs and lodges in a branch of the pulmonary artery, the fate of the lung rests on the adequacy of the bronchial collateral circulation.

The bronchial circulation originates from the aorta and nourishes the entire tracheobronchial tree down to the terminal bronchioles. The respiratory bronchioles, alveolar ducts and alveoli normally receive their oxygen and metabolic substrates from the pulmonary arterial circulation. At the junction of the terminal bronchi and respiratory bronchioles there is a rich anastomosis

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among capillaries supplied by both bronchial arteries and the pulmonary arteries. It has been shown that there is a reciprocal relationship between blood flow in the pulmonary arterial circulation and the bronchial circulation, so that if something happens to diminish the perfusing pressure in one avenue of circulation, flow through the other will increase. It follows, therefore, that if there is obstruction to the pulmonary arterial inflow, the bronchial arterial inflow will increase; and the viability of lung tissue subserved by the occluded pulmonary arterial circulation depends thus on the number and patency of the capillary communications.

When we consider pulmonary infarction, which represents ischemia and death of lung tissue, we must consider associated conditions that compromise the ability of the bronchial circulation to increase its blood flow and maintain the metabolic needs of the lung tissue formerly supplied exclusively by the pulmonary arteries. We must anticipate pulmonary infarction in the following three clinical conditions in which the bronchial circulation is often compromised:

1. Congestive heart failure. Presumably because of the increased pressure in the left ventricular or left atrium (into which much of the bronchial venous drainage occurs), there is a lower pressure gradient resulting in reduced blood flow through the bronchial circulation.

2. Chronic pulmonary disease. Changes in available pathways may result from attrition or destruction of bronchial capillaries in chronic pulmonary disease and may thereby prevent an increase in bronchial blood flow after pulmonary arterial occlusion.

3. Hypotension. The patient in shock has a reduced systemic arterial pressure and obviously cannot adequately perfuse blood through the bronchial circulation to maintain the nutritive requirements of an occluded portion of lung.

The incidence of pulmonary infarction following embolism is difficult to determine owing to lack of information about the total number of embolic events. Probably only 5 to 10 percent (or even less) of pulmonary emboli lead to infarction of lung tissue. The diagnosis of an infarct is usually easy since infarction causes characteristic symptoms, including pleuritic chest pain and hemoptysis, and is responsible for the parenchymal infiltrations and pleural effusions seen on x-ray films.

**TABLE 1.—Pulmonary Embolism: X-ray Findings**

Dilatation of Central Pulmonary Arteries
"Cutoff" of Peripheral Pulmonary Arteries
Right Ventricular Dilatation



**Figure 1.—Chest x-ray of a man with multiple pulmonary emboli showing dilatation of the main pulmonary arteries and right ventricular outflow tract, cutoff of branches to the right and left lower lung fields (arrows), and right ventricular enlargement.**

The diagnosis of pulmonary embolus is much more complicated because it does not produce death and ischemia of lung tissue; therefore, hemoptysis, chest pain, pleural effusion and the other classic features of infarction are absent. There are some well-recognized laboratory methods of identifying pulmonary embolism. The two most useful, and most widely advertised, are the electrocardiogram and the chest x-ray film. Table 1 lists the most valuable criteria for the diagnosis of pulmonary embolism by conventional chest x-ray studies, and Figure 1 shows an example of an advanced case. When the x-ray pattern of abrupt pulmonary artery termination and vascular dilatation is present, one should have no difficulty in making the diagnosis of multiple pulmonary emboli. When any of the characteristic x-ray findings are present, one should be very suspicious about pulmonary embolism. Unfortunately, x-ray films of the chest are often normal and of very little value in the diagnosis of the vast majority of the patients who have pulmonary emboli.

**TABLE 2.—Pulmonary Embolism:  
Electrocardiogram Findings**

S <sub>1</sub> Q <sub>3</sub> and S <sub>1,2,3</sub>
Inverted T Waves V <sub>1-3</sub>
Clockwise Rotation
Right Bundle Branch Block

**TABLE 3.—Pulmonary Embolism: Clinical Features**

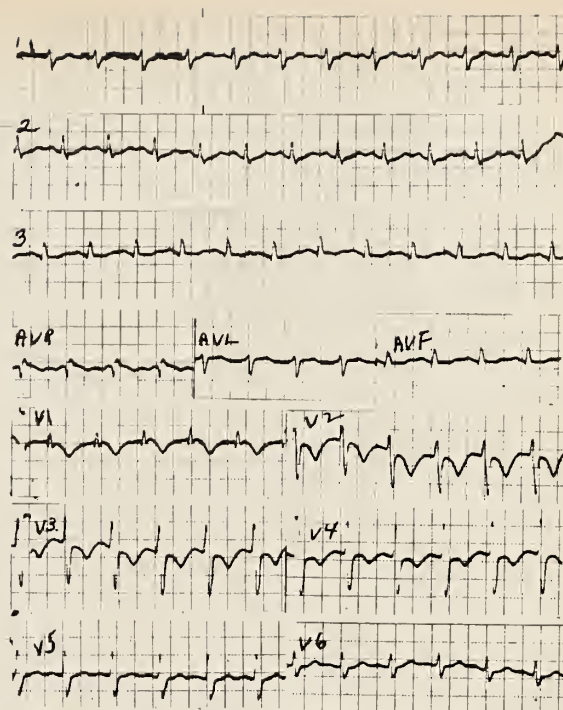
Central Nervous System: Anxiety, Restlessness, Syncope
Cardiac: Congestive Failure, Shock, Arrhythmias
Pulmonary: Hypoxia, Edema, Wheezing
General: Dyspnea, Fever

lism. If the changes are evident, fine; if they are not, one certainly cannot exclude the diagnosis.

The same considerations hold for the electrocardiogram. Table 2 presents the classic electrocardiogram criteria for acute pulmonary embolism, and Figure 2 shows a tracing from a patient with a classical pattern. If either this pattern or one of the other diagnostic EKG patterns is present, one should have no trouble in making the diagnosis of acute cor pulmonale—the most common cause of which is pulmonary embolism. I wish to emphasize again that, like the x-ray film, the EKG is very often nonspecific. It may, in fact, be normal in the presence of severe massive pulmonary embolism. Therefore, one cannot rely on it as a good technique for establishing the diagnosis.

Then how do we make the diagnosis of pulmonary embolism? Much has to be done on the basis of clinical suspicion. Table 3 lists the major manifestations of pulmonary embolism that can be related to involvement of three organ systems: the brain, the heart and the lungs. The central nervous manifestations may be prominent—in fact, sufficiently predominant to mislead the attending physician. Anxiety and restlessness are extraordinarily common in patients who have pulmonary embolism; syncope is related to the transient fall in arterial pressure, the mechanisms for which is discussed below. If syncope is prolonged, it can be associated with seizures; and occasionally, if the hypotension persists, focal areas of cerebral ischemia can develop so that the patient appears to have had a stroke.

The heart is involved both directly and indirectly. I have already mentioned acute cor pulmonale resulting from the sudden alteration in pulmonary arterial pressure. There are two mechanisms that act in concert to generate the increase in pulmonary arterial pressure. One of these is



**Figure 2.—Electrocardiogram of a patient with an acute pulmonary embolus showing S<sub>1</sub> Q<sub>3</sub>, inverted T waves V<sub>1-3</sub>, and clockwise rotation.**

the mechanical presence of the embolus in the pulmonary vasculature, so that there is an obstruction to part of the vascular pathways available to the blood flow. Since a pulmonary artery can be ligated in a normal individual without causing much, if any, elevation in pulmonary arterial pressure, it is generally believed that from 60 to 70 percent of the total cross-sectional area of the pulmonary vascular bed has to be obstructed before the pulmonary arterial pressure increases. Since the number and size of the pulmonary arteries involved (that is, the reduction in cross-sectional area of the vascular bed from occlusion) is often insufficient to account for a rise in pulmonary arterial pressure, other factors affecting blood vessels must be considered. Attention has been directed toward the possibility of pulmonary arterial vasospasm from either reflex or humoral stimuli.

Shock also seems to depend upon two mechanisms that act in concert and contribute to the fall in arterial pressures. One of these mechanisms is reduced cardiac output, which can be related in part to obstruction of the pulmonary vascular bed. In other conditions, a fall in cardiac output of the magnitude usually observed in pulmonary embolus is adequately compensated by peripheral



vasomotor reflexes which maintain arterial pressure. As these reflexes appear absent in pulmonary embolus, we infer that there is a second mechanism, mediated through reflexes, that causes systemic vasodilation. The fall in cardiac output, plus the vasodilatation, leads to the rather striking reduction in systemic arterial pressure. The fall in blood pressure leads to a reduction in cerebral perfusion and is undoubtedly the mechanism leading to the central nervous system abnormalities. Additionally, paroxysmal arrhythmias (usually supraventricular) can also accompany the lodging of a clot in the pulmonary vasculature.

A number of abnormalities related to pulmonary function also deserve comment. The most common of these is hypoxia, but its mechanism is still under some dispute; certainly it depends upon the development of a more generalized pulmonary abnormality than occurs in the lung subserved by the occluded vessel. In one study of patients with embolism, hypoxia resulted from a combination of ventilation-perfusion abnormalities and right-to-left shunting of blood.<sup>2</sup> Pulmonary edema has been reported in association with pulmonary emboli and may be due to arrhythmias or tachycardias induced in patients who have underlying heart disease. Interestingly, pulmonary edema has also been observed in patients without underlying heart disease, indicating that other mechanisms (to be discussed below) must account for more generalized changes in hydrostatic forces or vascular permeability.

Wheezing is also an occasional accompaniment of recurrent or single large pulmonary emboli.<sup>3</sup> The mechanisms for all of these—hypoxia, pulmonary edema, and wheezing—cannot be accounted for simply on the basis of a local phenomenon related to the clot in a branch of the pulmonary arterial system. The generalized nature of these responses implies that something else occurs which makes the remainder of the lung responsive to the embolic event. A number of factors have been proposed in an attempt to explain the generalized response. Dr. Jay Nadel<sup>4</sup> and co-workers of the Cardiovascular Research Institute here have demonstrated that histamine is released following emboli to the lungs. Dr. Julius Comroe<sup>5</sup> and others<sup>6</sup> believe that serotonin may be involved in some of the subsequent vascular and bronchial events that take place. Fibrinopeptides and other vasoactive substances are probably also released in the embolic process. Whether these

**TABLE 4.—Pulmonary Embolism: "Unusual Manifestations"**

Unexplained Hyperventilation or Dyspnea
Unexplained Fever
Fever Not Responding to Antibiotics
Increase in Severity of Congestive Heart Failure
Tachycardia, Digitalis Toxicity and Refractory Heart Failure
Unexplained Leukocytosis

**TABLE 5.—Pulmonary Embolism: Aids in Diagnosis**

Hints
Clinical Features
Electrocardiogram Changes
X-ray Changes
Moderately Useful
Perfusion Lung Scans
Pulmonary Function Studies
Diagnostic
Pulmonary Angiography

circulate through the vascular system and back to the lung, where they cause the generalized phenomena that I mentioned, or initiate various reflex mechanisms is uncertain at this stage. Neurohumoral processes of some sort must account for the diffuse pulmonary phenomena following a focal embolus.

Two of the most common clinical features of pulmonary embolus are dyspnea and fever (Table 3). Dyspnea is the most common symptom, and it could originate from abnormalities in the central nervous system, the cardiovascular system or the respiratory system. Regardless of its origin, dyspnea, particularly that which is recurrent or episodic, should call attention to the possibility of underlying pulmonary embolism. The most common sign is fever, which is usually low grade; but at times it may be 39.4° C (103.0° F) or higher and may have a hectic course that resembles the fever of sepsis. In a large series of cases with pulmonary embolism, fever was present in approximately 80 percent.<sup>1</sup>

The so-called "unusual manifestations" of pulmonary embolism<sup>7</sup> are listed in Table 4. Some of these features certainly relate to the patient discussed today. If a patient has a clinical condition favoring the formation of venous thrombosis (vascular injury, stasis, increased coagulability of blood) and then any of these clinical manifestations develops, the possibility of pulmonary embolism should be considered.

When pulmonary embolism is suspected, attempts should be made to establish the diagnosis. The relative value of the sources of diagnostic in-



Figure 3.—Perfusion lung scan with macro-aggregated albumin of the same patient whose x-ray is shown in Figure 1. Note the marked diminution of blood flow, shown by the absence of black dots, over the entire right lung and left lower lung field.

formation are given in Table 5. As I mentioned above, hints to the correct diagnosis are offered by clinical features, changes or chest x-ray findings. Additional more confirmatory, but still non-specific, evidence can be obtained by radioisotope lung scanning (Figure 3) and pulmonary function studies. The only definitive study, however, is pulmonary angiography.

It is tempting to believe that all filling defects seen on perfusion lung scans result from pulmonary arterial occlusive lesions, but such is definitely not the case. Disturbances in blood flow reflected by defects in perfusion lung scans are frequently encountered in patients with pneumonia and pleural effusion; the sites of involvement are usually those where infiltrations or fluid can be identified on the plain chest x-ray film. Vascular filling defects may also be seen when the plain film appears normal in patients with emphysema, bronchitis or asthma. In emphysema there is actually destruction of lung parenchyma and pulmonary capillaries to account for the vascular defects; however, in bronchitis and asthma the blood vessels are intact, but blood flow is redistributed away from regions of the lung where bronchospasm, secretions or edema impair ventilation. The latter conditions may be variable and evanescent, so even a changing lung scan is not pathognomonic of pulmonary emboli. Despite the nonspecificity of positive lung scans, a negative result is strong evidence against significant pulmonary embolism.<sup>8</sup>

In theory, pulmonary function studies should be of great help in the diagnosis of acute pulmonary embolism. We would suspect that since the lung supplied by an occluded blood vessel could not participate in oxygen uptake or carbon dioxide elimination, it would add what we call "wasted ventilation" or dead space. Simple tests could measure the extra amount of wasted ventilation or the difference in carbon dioxide tension between the patient's expired air at the end of expiration and in his arterial blood. (Normally there is no significant difference; and any increase at rest must be due to added dead space.) Although this analysis is theoretically attractive, the lung has a great capacity to redistribute blood flow and ventilation in response to reductions in either blood flow or ventilation to maintain "ideal" gas exchange. Therefore, when there is obstruction to blood flow, secondary changes in the bronchial walls, the smooth muscle of alveolar ducts, and the surface lining of the alveoli, all serve to prevent ventilation of the lung so that the carbon dioxide tension differences and increase in wasted ventilation may not be apparent. Pulmonary function studies in the resting patient are of little value because of the compensatory ability of the lung to redistribute ventilation when blood flow is impaired.

Dr. Nadel et al<sup>9</sup> have studied a large group of patients with pulmonary vascular occlusive diseases and have showed that the compensatory responses can be overcome by exercising the patient. Ordinarily when a subject exercises, his absolute value of wasted ventilation increases slightly, his tidal volume increases substantially, and his ratio of wasted ventilation to tidal volume decreases. When patients with pulmonary vascular diseases take deep breaths during exercise, they begin to ventilate the areas that were poorly ventilated at rest. The reason is that deeper breathing maneuver increases transpulmonary pressure and "opens" airways and alveoli that were "closed" when breathing at normal tidal volumes. Exercise testing is an extremely useful maneuver, and is one of the most sensitive tests available for the diagnosis of chronic pulmonary vascular occlusion. However, it is of little value in the clinical situations we are discussing because most of the patients in whom one is suspicious of pulmonary embolism are not suitable subjects for exercise studies.

The only way the definitive diagnosis of pulmo-





**Figure 4.**—Pulmonary angiogram of the same patient whose chest x-ray and lung scan are shown in Figures 1 and 3. Note the marked reduction in pulmonary arterial blood flow to the entire right lung and left lower lobe.

nary embolism can be made is by pulmonary angiography. (See Figure 4.) Routine angiography is only adequate for the detection of emboli in vessels down to 3 or 4 mm in diameter. Dr. Richard Greenspan, of the Department of Radiology at this hospital, has developed the use of small focal spots and magnification techniques that allow us to visualize blood vessels down to approximately 1 mm in diameter; and this adds a very important refinement to our ability to examine the sites and magnitude of pulmonary vascular occlusive disease. It is very important to do pulmonary angiography within the first 12 to 24 hours in the clinical course of a patient with suspected pulmonary emboli. Serial angiographic studies have shown that pulmonary emboli will lyse or fragment and move into smaller peripheral vessels very quickly; therefore, a negative angiogram two to three days after a suspected event does not tell you whether or not the patient had an earlier episode.

This entire discussion has emphasized early and accurate diagnosis so that treatment can be initiated. Available modalities of treatment are listed in Table 6. Many are based on the premise that

**TABLE 6.**—*Pulmonary Embolism: Treatment*

Anticoagulants
Heparin
Vena Cava Ligation
Urokinase
Surgical Removal

if you can keep emboli from recurring, the lung has a relatively good capacity—in fact, a surprisingly good capacity—to cope with the emboli that have already arrived there. The lung handles clots by fibrinolytic mechanisms that cause dissolution and fragmentation of clots and by recanalization of the vessels. Vessels that have been completely occluded can have blood flow restored and perform quite normally. Until recently the whole emphasis on treatment has been on prevention of further embolization by anticoagulants and surgical procedures. Now we have a new agent, urokinase, that may accelerate and augment the dissolution of emboli in the lung and the thrombus in the peripheral vessel. A cooperative study is evaluating the results of trials of urokinase, and although preliminary results are encouraging, the final results are not yet available.

DR. SLEISENGER: Thank you, Dr. Murray, for that complete and concise summary of pulmonary embolism and infarction.

A PHYSICIAN: Is occlusion of the bronchial arterial circulation responsible for infarction?

DR. MURRAY: It is very difficult to assess accurately the magnitude of bronchial blood flow and its distribution. Its role in pulmonary infarction is largely inferential. Pulmonary infarcts develop in clinical circumstances in which there is suggestive evidence of an impairment of bronchial circulation; but solid documentation has not been obtained. The normal role of the bronchial circulation remains obscure, as evidenced by lung transplantation studies. Removal of a lung from an animal and reimplantation completely interrupts all of the bronchial blood flow, and yet nothing adverse appears to happen to the airways. Perhaps their metabolism is maintained by retrograde flow from the pulmonary arterial circulation, but no one yet knows why the lung survives. A RADIOLOGIST: Recent observations by Dr. John Austin and Dr. Stuart Sagel in the Department of Radiology here may be relevant to the wheezing described in the patient presented. In their studies of experimental pulmonary embolism, they used a small focal spot tube and direct 10-fold magnification after tantalum bronchography. They have shown rather striking and dramatic

constriction of bronchi all the way down to the very small bronchial level, both ipsilateral and contralateral to unilateral pulmonary emboli.

DR. MURRAY: That is an interesting observation that could relate to the ventilation-perfusion abnormalities which lead to hypoxia as well as to wheezing resulting from bronchoconstriction.

#### TRADE AND GENERIC NAMES OF DRUGS

Coumadin® .....sodium warfarin

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#### TRACHEOTOMY HAZARDS IN TRAUMA TO THE TRACHEAL-LARYNGEAL REGION

"Car accident victims can sometimes have a tremendous amount of damage to the laryngeal-tracheal complex with very little superficial evidence, that is, in the soft tissues of the neck. The point is that tracheotomy is not the real solution. If a tracheotomy is necessary, then endeavors should be made immediately to find out why. . . . So often in these cases, the tracheotomy is performed by someone who is not particularly knowledgeable about this type of injury, and that is the end of it until he tries to extubate the patient. Then he finds that he's in trouble because of obstruction. . . .

"Another reminder: when patients with acute laryngeal trauma come to the emergency room and tracheotomy is necessary, one must splint the neck; movement must be minimized."

—G. SLAUGHTER FITZ-HUGH, M.D., Charlottesville, Va.  
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 17, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



## Hara-kiri and Its Consequences

HARA-KIRI AS EVERYONE KNOWS is the act by which a person commits suicide by disemboweling himself. Quite often this is done with some ceremony and more or less in public. There is reason to believe that organized medicine in California may be about to commit this act and even do it more or less publicly.

Whether by contrivance or not, petitions were circulated within a short space of time in several of the major component medical societies of the California Medical Association calling for local referenda on the question of whether or not membership in the California Medical Association and the American Medical Association should be required of a physician who chooses to join his county medical society. Whether by accident or design, these petitions were circulated so that the balloting occurred close to the time the bills for medical association dues were received by the membership. In each instance the vote was couched in terms of *free choice* versus *compulsion*, and in each instance the majority quite predictably expressed themselves in favor of free choice and against compulsion. When this issue is given to physicians, the response always has been and probably always will be the same. In view of these local polls the CMA House of Delegates has now directed that there be a statewide opinion poll of the CMA on this issue, and this is scheduled to take place September 1.

Unfortunately the real question is not the one that is being asked. It is not whether we favor free choice or voluntarism as against compulsion or control. The real question is whether the medical profession is to be able to present a strong

and united front through a strong and all-embracing professional organization, or is to be weakened, divided and rendered ineffectual. There are obviously those within and outside the professional ranks who would very much like to see this happen, curiously for opposite reasons, since those within the profession are apt to feel the organization has not been effective to their liking and those outside may consider it to have been more effective than they would wish, and at times perhaps even a thorn in their side. What is now happening, whether by intent or not, is that the profession is going to be asked to answer one question and in so doing it will decide another. The fact is that in voting on the issue of voluntary or compulsory membership in the CMA, the membership will really decide whether the CMA is to have a go at disemboweling itself, and this more or less in the public view.

At present the CMA is a force to be reckoned with in the State of California and its influence is of growing importance in the AMA and in the nation. This is not the case with many other, weaker, state medical associations. The CMA effectiveness rests not only on its leadership and staff, which have been far above average in skill and dedication, but much more importantly upon the solid and tangible support of the membership. This is the root source of all political influence and also the power to persuade. And in these times persuasion and political power and influence are not things to be lightly discarded.

If there is now to be a substantial defection of physicians from CMA membership, whether because of personal dissatisfaction with what has or has not been accomplished, unhappiness with dues, or an in-principle dislike of *compulsion* to join, the inescapable result will be a considerable weakening of CMA influence and effectiveness at a most critical moment in the revolution in health care which is occurring in both state and nation. If this happens, physicians may find themselves without an organization capable of speaking authoritatively and effectively for the profession. The need to do something about this will quickly

become apparent, and probably soonest in the field of economics. It is here that the weakness of the organized profession will be first felt since advantage would be quickly taken of it. An organizational alternative would soon be sought. It seems more than likely that some form of unionization of the profession would occur, with all that this implies, simply as a matter of self-defense. There is ample and growing precedent for unionization and use of union tactics in the health care industry. If organized medicine as it now exists fails of support from its members and becomes ineffective, it would seem inevitable that social, economic and political forces will close in and drive the profession, however reluctantly, into some kind of a strong union which the members themselves might or might not be able to control. An economic oriented union would signal the end of medicine as a profession.

If these are to be the kinds of consequences, it is the opinion of this writer that the physicians of California would be well advised in these times to avoid hara-kiri for a medical organization that has so far served them quite well and perhaps much better than they are aware.

—MSMW

## Transaminasemia: Semantic Confusion of A Clinical Dilemma

ELEVATED SERUM TRANSAMINASE levels found on a "routine" serochemical graph during investigation of the patient with malaise, or persisting after a bout of acute hepatitis, presents the clinician with a diagnostic question—chronic hepatitis? The conscientious physician, examining the pertinent literature, will be deluged by hepatological semantics ranging from *transaminitis* (a non-disease?) through *autoclastic hepatitis* (a fortunately self-destroyed term) to lupoid hepatitis (possibly a misleading misnomer).

In the Specialty Conference elsewhere in this issue, Goldstein and his colleagues in clinical hepatology and pathology attempt to bring some or-

der from this chaos. They emphasize the difficulty of definition. Although not unanimously in agreement, most hepatologists will accept transaminase elevations persisting over ten weeks as indicative of chronic hepatitis regardless of other clinical features.

What the clinician wants to know is, what is the practical approach to the diagnosis and prognosis in such a patient? The most helpful studies are:

1. *Clinical Stigmata*. The presence of firmness of the liver, splenomegaly, spider angiomas, ascites or varices adds disturbing prognostic significance, suggesting progression to cirrhosis has already occurred.

2. *Hyperglobulinemia* reflects the presence of increased numbers of chronic inflammatory cells in the liver (plasma cells and lymphocytes), although these are not the only source of the abnormal amounts of serum globulin. The degree of abnormality of the gamma globulin correlates roughly with the severity of inflammatory cell infiltrate and is an important clinical clue to the presence of chronic hepatic disease.

3. *Hepatitis associated antigen* (HAA, Australia antigen) is transient in the majority of patients with initially HAA-positive acute hepatitis. The reaction for HAA remained positive in only 4.5 percent of Redeker's patients. Persistent antigenemia (greater than four months' duration) is more common in patients with impaired immunity (chronic hemodialysis, lymphoma, leukemia) and is usually associated with evidence of a variable degree of continuing liver injury. Although a patient recovering from viral hepatitis may have persistent antigenemia without biochemical abnormality or progression to cirrhosis, Redeker emphasized that in all his patients with acute hepatitis progressing to cirrhosis the HAA reaction was acutely and chronically positive; no HAA-negative adult hepatitis progressed to cirrhosis, in his experience. Any case that did progress from acute hepatitis to cirrhosis did so quickly, within 12 to 18 months.

Therefore, HAA has important diagnostic and prognostic significance in the patient with persistent transaminasemia after acute viral hepatitis. If the patient is HAA-negative, or is HAA-positive and cirrhosis has not developed by 18 months, his prognosis probably is good.

4. *Serology*. A host of abnormal serologic reactions (many of which are "false positive") and tissue antibodies have been reported in various



forms of chronic active hepatitis. The most useful of these are the lupus erythematosus (LE) cell phenomenon and the smooth muscle antibody (SMA). Experience has shown no clinical difference between SMA-positive patients with LE cells and those without. These probably are identical disease states, commonly have extra-hepatic "systemic" abnormalities (arthralgias, rashes, fever, acne) and form the "lupoid" sub-group of chronic active hepatitis. As suggested by Reynolds et al, it probably is of value at present to distinguish these patients from those of the other clinical subgroups—that is, from chronic active viral hepatitis (HAA-positive, SMA-negative and LE-negative) with its possible progression to hepatoma; from chronic active toxic hepatitis (with a history of oxyphenisatin exposure) and chronic active hepatitis immunologically and HAA-negative and likely a collection of multiple causes of chronic hepatic disease. Any of these can and frequently does progress to post-necrotic cirrhosis.

**5. Liver Biopsy.** A definitive diagnosis of chronic active hepatitis cannot be made without liver biopsy. Although the clinical and laboratory features outlined above allow a provisional diagnosis in the transaminasemic patient, the differentiation of this disorder (with its attendant high morbidity and mortality) from benign acute viral hepatitis and persistent ("unresolved") hepatitis requires tissue examination. In contrast to the predominantly centrilobular and focal intralobular hepatocytolysis of ordinary viral hepatitis, the chronic active hepatitis lesion is characterized by perilobular parenchymal cell necrosis with destruction of the limiting plate, striking chronic inflammatory cell infiltration in these areas of necrosis, and varying degrees of fibrosis, progressing to cirrhosis. The various clinical forms of chronic active hepatitis (lupoid, viral, toxic) are histologically indistinguishable.

"Subacute hepatic necrosis" (SHN) is a recently described lesion<sup>1</sup> seen in clinically severe cases of acute viral hepatitis, and it frequently (37 percent of Klatskin's series) progresses to post-necrotic cirrhosis, sometimes via the histology of chronic active hepatitis. Klatskin's data suggests that only "serum hepatitis" cases of SHN progress to cirrhosis. The hallmark lesions are broad zones of hepatic necrosis and collapse bridging adjacent portal triads or central veins, or both. It deserves special attention as another ominous prognostic finding in a case of transaminasemia.

The foregoing features allow the clinician to classify a case of transaminasemia. What treatment is indicated? Acute and unresolved hepatitis require only supportive care. The difficult decision relates to the case of chronic active disease. Detailed discussion of treatment, which is beyond the scope of this review, has been presented elsewhere.<sup>2</sup> Immunosuppressive agents (in anti-inflammatory doses) and steroids offer significant reduction of morbidity and of early mortality, but in most cases provide no improvement of the unrelenting histologic progression to cirrhosis. Evidence that immunosuppression may unfavorably affect the prognosis of one form of experimental acute viral hepatitis<sup>3</sup> compels us to evaluate this treatment further, particularly in HAA-positive chronic active hepatitis.

The epidemiology of HAA has been reviewed in detail in these pages previously<sup>4</sup> and elsewhere.<sup>5</sup> Its discovery opened a new chapter in hepatitis research. It has compelled us to discard our previous concepts of serum and infectious hepatitis; we should now refer to HAA-positive and HAA-negative hepatitis, either of which may be transmitted orally or parenterally. It will revolutionize blood banking, requiring mass pre-screening of all donor units before they are administered. Transfusion of an HAA-positive unit carries with it an estimated 75 percent risk of development of icteric hepatitis, HAA positivity, or antibodies to HAA. Transfusion of HAA-negative blood carries an approximate 10 percent risk of development of mild anicteric hepatitis. This may in part reflect transfusion of blood with a very low-titer HAA positivity, which is undetectable by current methods, since a 1:10,000 dilution of HAA-positive serum remains infective although the HAA test becomes negative. There may also be a third type of viral hepatitis which has its own antigens. Other observers have estimated that the hazard of hepatitis developing from HAA-positive blood is 12 times that of HAA-negative blood, and that blood from commercial donors is 10 to 12 times as likely to be contaminated as blood from volunteers. Of additional importance is the recent observation that an adult with acute HAA-positive hepatitis has a 5 percent chance of becoming a chronic HAA carrier, a child 5 to 10 years of age a 30 to 50 percent chance, and a one-year old a 70 percent chance.

Further studies have shown that gamma globulin does not neutralize the infectivity of HAA-posi-

tive serum. Clinical confirmation of this comes from studies demonstrating no reduction in the incidence of serum hepatitis in cardiac surgery patients who were given gamma globulin prophylactically.

These studies represent only the tip of the HAA iceberg. The future lies in such directions as the genetics of HAA persistence in normal populations (tropical countries), in immuno-deficient individuals (leukemia, transplant patients) and possibly in malignant hepatoma.<sup>6</sup> The pathogenicity of HAA for other organs has been hinted at by the recent description of HAA-positive periarteritis with localization of the virus particles in blood vessel walls. We are even hearing the first whispers of a serum hepatitis vaccine.

But what of the semantic chaos with which we began? Perhaps we can agree for now to broadly classify the patient with transaminasemia of hepatocellular origin as:

#### A. Acute Hepatitis

##### 1. Viral

- (a) HAA-positive
- (b) HAA-negative
- (c) Subacute hepatic necrosis (HAA-positive or HAA-negative).

##### 2. Non-Viral

#### B. Chronic Hepatitis

##### 1. Unresolved viral hepatitis

##### 2. Chronic active hepatitis

- (a) Viral (HAA-positive)
- (b) Lupoid (HAA-negative; LE positive or negative; SMA-positive)
- (c) Idiopathic (HAA-negative; LE-negative; SMA-negative)
- (d) Toxic (oxyphenisatin).

##### 3. Other hepatotoxins and disease states with secondary liver involvement.

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## Neutrophils and Host Defense

THE COMPREHENSIVE ARTICLE by R. I. Lehrer in this issue of CALIFORNIA MEDICINE focuses attention on the role of the leukocyte in host defense against microbial agents. The suggestion by Mechnikoff that "the essential and primary element in typical inflammation consists in a reaction of the phagocyte against a harmful agent" remains as valid today as when proposed before the turn of the century. The leukocyte is assisted in its task by many other factors. The importance of the leukocytes, however, is emphasized by the frequency and severity of infections in patients with agranulocytosis and by the presence of a group of conditions in which an increased susceptibility to infection is associated with impaired intraleukocytic microbicidal activity.

The process of phagocytosis effectively isolates the organism from the extracellular environment in a vacuole lined by the invaginated cell membrane. Phagocytosis *per se* does not appear to be harmful to the ingested organism; indeed, organisms sequestered within the phagocytic vacuole but not killed by cellular systems are protected from extracellular antimicrobial systems and from certain antibiotics. However, phagocytosis is associated with a burst of metabolic activity and the release of toxic substances from the cytoplasmic granules into the phagocytic vacuole. Death and degradation of the ingested organisms follow. The microbicidal systems consist of products of leukocytic metabolic activity such as acid and  $H_2O_2$ , granular components with no known enzyme activity, such as certain cationic proteins (phagocytin, leukin) and granular components with enzyme activity, such as lysozyme and myeloperoxidase. Myeloperoxidase is a component of a complex microbicidal system which also requires  $H_2O_2$  and an appropriate oxidizable cofactor such as iodide, bromide, chloride or thiocyanate ions and is facilitated by the acid pH which is believed to exist in the vacuole. The ingested organisms



vary in their susceptibility to the intravacuolar microbicidal systems; some organisms (pneumococci, for example) are rapidly killed by acid whereas others (such as lactobacilli) are acidophilic; some are readily lysed by lysozyme whereas most organisms resist the action of this enzyme unless previously damaged, as, for example, by antibody-complement; some organisms (such as streptococci, pneumococci, lactobacilli) secrete  $H_2O_2$  into the intravacuolar space and thus contribute to their own destruction by  $H_2O_2$ -dependent systems whereas others (certain Gram-negative pathogens, gonococci, staphylococci) contain catalase which breaks down  $H_2O_2$ . As a result of this highly complex interrelationship, certain organisms are killed more readily by leukocytes than others and the effective antimicrobial system may vary with the type of organism and with the functional state of the leukocyte. In a typical *in vitro* experiment 99 to 99.9 percent of streptococci or pneumococci are killed in one hour by isolated leukocytes under conditions in which approximately 90 percent of staphylococci and 30 to 50 percent of *Candida albicans* are killed.

Defects in the intraleukocytic microbicidal systems exist which result in the prolonged intracellular survival of ingested organisms. A beginning in the classification of these conditions according to the molecular lesion can be made. The leukocytes of patients with chronic granulomatous disease have impaired microbicidal activity and decreased phagocytosis-induced glucose carbon 1 oxidation,  $H_2O_2$  formation, nitroblue tetrazolium reduction and iodination. The importance of the decreased  $H_2O_2$  formation to the defect in microbicidal activity has been emphasized by the partial reversal of the lesion by the introduction of a  $H_2O_2$  generating system into the cell. A degranulation defect also has been suggested. Although degranulation does occur in these cells, it is possible that the rate of degranulation may be abnormal under certain conditions. The result is repeated and severe infections. The  $H_2O_2$  deficiency syndrome, if this is the basic defect, may arise from a variety of primary enzyme lesions affecting the formation of  $H_2O_2$  and its availability for the microbicidal act. The demonstration of a leukocyte functional defect comparable to that of the classical x-linked variety of chronic granulomatous disease in patients with atypical histories (non x-linked variety of chronic

granulomatous disease, familial lipochrome histiocytosis,<sup>1</sup> absent leukocyte glucose-6-phosphate dehydrogenase<sup>2</sup>) attests the heterogeneity of this group. A microbicidal defect could not be demonstrated in the leukocytes of the two original patients with Job's syndrome,<sup>3</sup> which suggests that this condition may not be a variant of chronic granulomatous disease as suggested by Bannatyne et al.<sup>4</sup>

Another leukocytic lesion associated with impaired microbicidal activity is myeloperoxidase deficiency. Myeloperoxidase deficiency may be hereditary or acquired. Patients with hereditary myeloperoxidase deficiency have leukocytes with decreased fungicidal and bactericidal activity although the microbicidal defect is not as severe as in chronic granulomatous disease. These patients are relatively free of infection. Of five patients with hereditary myeloperoxidase deficiency, one had systemic candidiasis while the remainder were in good health. A second patient with candida infection and an absence of myeloperoxidase from the majority of peripheral neutrophils was reported in the article by Lehrer in this issue; however, it is not clear whether the lesion in this instance was hereditary or acquired. A reversible decrease or loss of myeloperoxidase from some or all leukocytes has been reported by Sato<sup>5</sup> in epidemic encephalitis Economo, and by Graham<sup>6</sup> in severe bacterial infection. Graham, in the pre-antibiotic era, followed the decline in neutrophil peroxidase in a patient with pneumococcal pneumonia; 96 percent of neutrophils contained no peroxidase by histochemical staining at the time of death. These findings suggest that myeloperoxidase deficiency may be a consequence of, as well as a cause of, infection. Certain agents which inhibit peroxidase-catalyzed reactions inhibit the microbicidal activity of normal leukocytes but have no effect on peroxidase-negative leukocytes.<sup>7</sup> This, and the decreased microbicidal activity of peroxidase-negative leukocytes, suggests the involvement of peroxidase in the microbicidal activity of normal cells. The relative freedom from infection in hereditary deficiency may be due to an overkill capacity of the leukocytes for most organisms, which allows them to function adequately under most circumstances even when the total microbicidal potential is decreased. Further, an increase in the activity of the non-peroxidase antimicrobial systems may compensate for the decrease in peroxidase-mediated systems.<sup>7</sup>

The complexity of the intraneutrophilic microbicidal systems and their importance in the host defense is emphasized by the studies of rare in-born errors of metabolism such as chronic granulomatous disease and hereditary myeloperoxidase deficiency. Certainly it might be expected that more subtle changes in leukocyte function introduced by therapy, diet or coexisting disease also may influence the course of infection.

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## ABDOMINAL ANGINA

"The onset of symptoms [in patients with intestinal ischemia due to mesenteric arterial disease] is a late phenomenon and indicates rather far advanced vascular disease. Many patients with such limitation of their mesenteric blood supply are asymptomatic and when there is abdominal angina, weight loss, etc., it usually heralds impending catastrophe and constitutes a fairly urgent indication to proceed with diagnosis and therapy. Of the 17 patients we saw with abdominal angina, none had had symptoms for longer than two years and 12 of the 17 had either acute infarction or definitive surgery within six months of onset of their abdominal angina.

"In conclusion, I think some patients may survive acute intestinal ischemia with successful embolectomy and arterial reconstruction. But when arterial occlusive disease exists, the occurrence of symptoms is a very late phenomenon, and the best hope for improved results lies in prompt recognition of chronic ischemic symptoms and elective revascularization before acute ischemia develops."

—GARLAND D. PERDUE, JR., M.D., Atlanta  
Extracted from *Audio-Digest Surgery*, Vol. 16,  
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# CASE REPORTS

## Infectious Complications of Intravenous Polyethylene Catheters

GERARD R. FREDRICK, M.D., AND  
LUCIEN B. GUZE, M.D., *Los Angeles*

INTRAVENOUS POLYETHYLENE CATHETERS were first utilized in clinical medicine in 1945.<sup>1,2</sup> They have been used to provide a practical avenue for fluid, electrolyte and antibiotic administration, blood replacement and venous pressure monitoring. While at first believed to be indicated only when there was no ready access to a patient's veins by direct needle puncture of superficial veins, more recently they have been used almost routinely as either percutaneous polyethylene catheters or as surgical venous cutdown catheters.

For a time they were thought to involve no serious complications,<sup>2,3,4</sup> but now problems of many types have been related to their use—phlebotrombosis,<sup>3,5,6,7</sup> thrombophlebitis,<sup>7,8</sup> phlebitis,<sup>6,9,10</sup> septic phlebitis,<sup>5,6,11</sup> cellulitis and abscess formation,<sup>6,9,12</sup> bacteremia and septicemia,<sup>5,10,12</sup> bacterial and fungal endocarditis,<sup>13</sup> pulmonary embolism,<sup>5</sup> catheter embolism,<sup>14,15,16</sup> and cardiac perforation.<sup>15</sup> Recently, we saw a patient whose case emphasized several of these complications.

### Report of a Case

The patient was a 50-year-old man who was admitted to Harbor General Hospital July 1, 1968, for evaluation of suspected dermatomyositis. This

diagnosis was confirmed by muscle biopsy and he was treated with prednisone, 30 mg twice a day. Subsequent hospital course was complicated by intermittent upper gastrointestinal bleeding from a duodenal ulcer, observed on x-ray study, and by intermittent fever. On the 16th hospital day, an intravenous polyethylene catheter was inserted to facilitate blood and fluid replacement. Seventy-two hours later the intravenous catheter was removed because of leakage of fluid at the cutdown site and a new intravenous polyethylene catheter was inserted. This second catheter remained in place until eight days later, the 27th hospital day, when fluid was found to be leaking from it into surrounding tissues. At this time, the patient was found to be hypotensive (blood pressure 70/40 mm of mercury) and to have oral temperature of 40.6°C (105°F). Physical examination, urinalysis and chest x-ray failed to reveal any localized infectious process. Cultures of blood, material from the cutdown site, the polyethylene catheter tip, urine and sputum were prepared, and the administration of cephalothin, 3 grams intravenously every six hours, and kanamycin 500 mg intramuscularly every 12 hours, was begun. A new intravenous polyethylene catheter was placed at a different site in the same arm. The hypotension responded promptly to intravenous fluid administration but remittent fever continued during the next six days. At that time the cultures obtained on the 27th hospital day showed growth of *Serratia* species on the blood, the cutdown site material and the catheter tip. The urine culture showed no growth and the sputum culture grew normal flora. Antibiotic sensitivities of the organisms cultured are shown in Table 1.

On the 33rd hospital day the last intravenous cutdown site was observed to be grossly infected. There was purulent material in the cutdown wound and in the intravenous catheter. Cellulitis surrounded the catheter site. The catheter was removed and the site of insertion debrided.

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**TABLE 1.—Antibiotic Sensitivities of *Serratia* species\* cultured in present case**

Antibiotic	Minimum Bactericidal Concentration (µg/ml)	Minimum Inhibitory Concentration (µg/ml)
Gentamicin	12.5	6.25
Ampicillin	>100	100
Tetracycline	>100	100
Streptomycin	25	12.5
Kanamycin	25	12.5
Penicillin G	—	>100
Cephalothin	—	>100
Colistin	—	>100
Chloramphenicol	—	>100

\*Identified by currently accepted methods.<sup>17,18</sup> Antibiotic sensitivities were obtained by tube dilution techniques.<sup>19</sup>

Eight hours later the patient was afebrile and remained so throughout the rest of his hospital stay. Twelve blood cultures done serially after the debridement showed no growth.

This case illustrates several complications related to intravenous polyethylene catheter usage—namely, cellulitis and abscess formation at the cutdown site and bacteremia and septicemia originating from the intravenous catheter.

In articles describing infections related to use of intravenous catheters, staphylococci are the organisms most commonly incriminated (68.4 percent in one series<sup>20</sup>), although various Gram-negative rods are frequently found,<sup>8,10,12,20-24</sup> and fungi rarely.<sup>8,13,25,26</sup> Infectious complications have been variously ascribed to the introduction of organisms into the cutdown wound at the time of insertion,<sup>10,21</sup> to contamination during wound care,<sup>10,21</sup> to contamination of intravenous fluids<sup>27,28</sup> and to bacteremia from other areas seeding the catheter site.<sup>10</sup> Mechanical shearing of endothelial lining of the vein by inevitable motion of the catheter, followed by formation of a small fibrin clot, may serve as a locus for trapping and multiplication of bacteria.<sup>29</sup> Previous reports have pointed out the lack of correlation between clinical phlebitis and infection<sup>10,21</sup> (which was probably the situation in the present case on the 27th hospital day when there was no apparent infection at the cutdown site), but all subsequent bacteriologic and clinical information points to the cutdown site as the source of bacteremia and septicemia.

A number of studies have shown that intravenous polyethylene catheters are frequently associated with bacteremia acquired in a hospital environment, being inculpatated in 9 percent to 43 percent of nosocomial infections.<sup>12,20</sup> In one

study bacteremia developed in 0.7 percent of patients with catheters in place more than 24 hours and in 2.5 percent of those who had them in place more than 48 hours.<sup>20</sup> Most cases of catheter-related bacteremia have occurred after the catheter has been in place for at least 48 hours.<sup>10-12,20,30</sup> Moran and coworkers<sup>21</sup> showed that when Neosporin® ointment was applied daily, cultures of catheter tips were negative in a far higher proportion of cases. However, these findings were not completely confirmed by other investigators.<sup>31,32</sup>

In view of our personal experience and that of others as reported in the literature, a number of rules for the use of intravenous polyethylene catheters are recommended:

- Catheters should be used only when deemed vital to the patient's welfare—that is, only if the patient does not have satisfactory superficial veins for direct infusion through a needle or when central venous monitoring is essential to care.
- Surgical cutdowns and intracatheter placement must be performed under conditions of complete asepsis with firm anchoring of the catheter to the arm.<sup>33</sup>
- The cutdown wound dressing must be changed daily, with application of Neosporin® ointment at the site of entry, inspection of the wound for sepsis and inspection of the extremity for indication of phlebitis.
- If evidence of sepsis appears, the cutdown catheter must be removed and culture of material from it prepared promptly. In addition, cultures of blood for fungi and aerobic and anaerobic bacteria should be carried out.
- Regardless of circumstances, the intravenous polyethylene catheter should be removed at the end of 48 hours, for leaving it in place longer greatly increases the risk of most complications, especially infections. If a catheter is still needed after that, a new one may be inserted at a different site.

## Summary

A case is presented in which infection due to *serratia* species at the site of insertion of an intravenous polyethylene catheter, bacteremia and septicemia complicated the course in hospital of a patient receiving blood and fluid replacement therapy. Guides are given for avoiding infection in such circumstances and for detecting it early should it develop.



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## Primary Hyperparathyroidism

Two Cases—Carcinoma and Adenoma—  
In a Small Hospital

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SINCE ASKANAZY first described an abnormal parathyroid in 1904,<sup>1</sup> several types of parathyroid disease have been delineated. Because of the protean symptoms associated with it, primary parathyroidism is frequently not considered in diagnosis until the clinical manifestations have completely developed or serum calcium is determined fortuitously, as it was in the two cases here presented. In both cases the patients were admitted for reasons other than primary hyperparathyroidism, and elevated serum calcium levels were discovered on routine admission Chemistry Panel 12 (Technicon SMA 12-60) determinations.

Numerous follow-up studies of primary parathyroid disease make the point that adequate correlation of surgical and pathologic findings during operation can lead to appropriate curative surgical operation.<sup>2-6</sup> All too often this correlation is not made until after the procedure is finished, necessitating further operation later.

This presentation will emphasize routine Chemistry Panel 12 admission analyses<sup>7</sup> and the close correlation of pathologic and surgical findings at the time of the first exploratory surgical procedure for primary parathyroid disease.

## Reports of Cases

Case 1. A 68-year-old white woman was admitted to hospital October 1 1969 for elective repair of a right femoral hernia. Constipation and vague bone discomfort had been present for some years. On physical examination no masses were palpated in the neck. A preoperative Panel 12 (SMA 12-60) determination revealed calcium of 16 mg per 100 ml. Phosphorus was 1.9 mg per 100 ml and alkaline phosphatase was 90 millimoles per ml. Blood urea nitrogen was 17 mg per 100 ml and total protein was 6.9 grams, of which albumin was 4.5 grams. Creatinine was 1.9 mg per 100 ml

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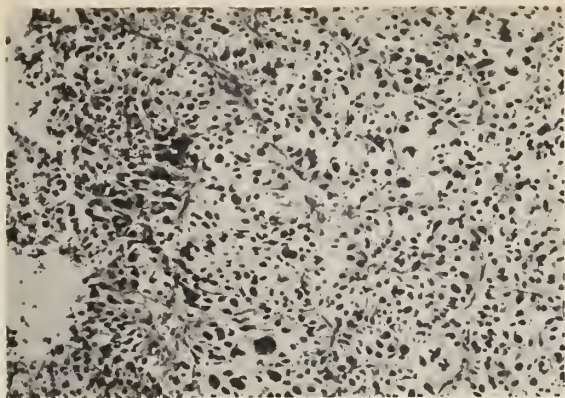


Figure 1.—Parathyroid carcinoma, showing pronounced cellular pleomorphism and trabecular pattern (x250).

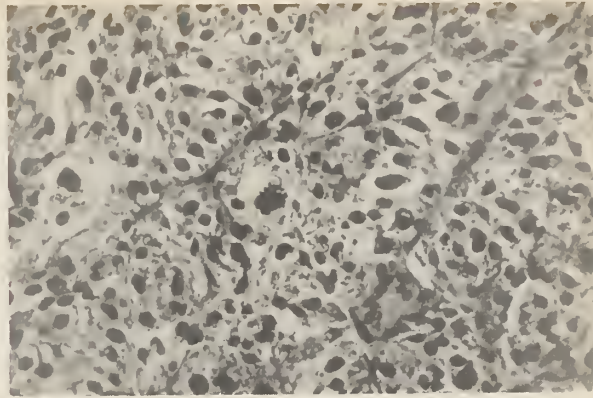


Figure 2.—Parathyroid carcinoma, showing trabecular-glandular pattern with a centrally located abnormal mitotic figure (x400).

and tubular resorption of phosphate was 40 percent (normal 80 to 90 percent). Prednisone was given, 40 mg a day for 5 days. The serum calcium remained elevated at 15.6 mg per 100 ml.

Radiographs of the phalanges revealed subperiosteal resorption in the distal portions of the proximal and midphalanges.

On October 11 an exploration of the neck was performed and a large, rubbery firm, brown-tan mass was found in the left side of the neck, partially compressing the thyroid gland. The tumor was somewhat adherent to the recurrent laryngeal nerve and adjacent tissue, but no frank invasion was noted. A frozen section of the lesion was prepared and the other glands were identified and left intact.

The postoperative course was unremarkable for several days until the serum calcium dropped to 8.4 mg per 100 ml and the patient began to have signs of tetany and paranoid delusions.<sup>8</sup> Treatment was begun immediately with calcium gluconate intravenously and large doses of calcium by mouth, and the serum calcium slowly reverted to normal. The patient was discharged October 19, and all paranoid delusions slowly cleared. Serum calcium remained normal for 12 months, then increased to 13.5 mg per 100 ml.

*Pathologist's Report.* The specimen consisted of a 5 by 4 cm irregularly shaped, rubbery firm, brown-tan mass appearing roughly encapsulated. Cut section revealed a variegated appearance with areas of yellow-tan blending with brown-tan. Fibrous trabeculae were seen streaking throughout the parenchyma. The total weight of this specimen was 13.5 grams. Microscopically (Figures 1 and 2) the tumor was consistent with para-

thyroid origin and had a decidedly variegated appearance. Some areas showed fairly regular cells with small, oval, somewhat hyperchromatic nuclei with eosinophilic cytoplasm. Most of the microscopic fields showed large, fibrous septae scattered throughout the parenchyma. These fibrous trabeculae separated the tissue into a glandular, trabecular pattern with individual cells showing pronounced pleomorphism with spindle-shaped nuclei and hyperchromatism containing numerous atypical mitotic figures.<sup>9</sup> Distinct invasion of the capsule was seen in numerous sections.

Case 2. A 68-year-old white woman, a retired school teacher, was admitted to hospital October 28 1969 for evaluation of severe lower extremity cramps, increasing constipation and lethargy. No abnormality was noted on physical examination, and no masses were palpated in the neck. An x-ray film of the chest, sigmoidoscopic examination and radiographic examination of the upper and lower gastrointestinal tract were negative. Panel 12 (SMA 12-60) studies revealed serum calcium of 13 mg per 100 ml. Phosphorus content was 2.3 mg and urea nitrogen 23 mg per 100 ml. Total protein was 6.9 grams per albumin 4.2 grams, alkaline phosphatase 51 millimoles per ml. The serum creatinine was 1.1 mg per 100 ml. Tubular resorption of phosphate (TRP) was calculated at 83 percent by using the formula:

$$\text{Percent TRP} = 100 \frac{(1 - \text{VP} \times \text{SC})^{10}}{(\text{VC} \times \text{SP})}$$

where P = inorganic phosphate concentration (mg per ml)

c = creatinine concentration (mg per ml)

s = serum

v = volume in ml



By the method of Chambers et al,<sup>10</sup> calcium was infused in the amount of 15 mg per kilogram of body weight over a four-hour period. Tubular resorption was measured again and the results showed a flat response with no appreciable change in the TRP rate, indicating an autonomous secretion of parathyroid hormone. Prednisone suppression, 40 mg a day for five days, was carried out and the serum calcium remained elevated at 13.1 mg per 100 ml.

On November 7 1969, surgical exploration of the neck was carried out, and a well encapsulated, chocolate brown mass was removed from the right side of the neck. The mass appeared encapsulated and not adherent to any of the adjacent structures. A frozen section of the lesion and a biopsy specimen and frozen section of a normal parathyroid were prepared. A diagnosis of parathyroid adenoma was then submitted. The post-operative course was uneventful and the patient was discharged November 12 1969. The serum calcium levels thereafter remained within normal limits and the bone discomfort and constipation were relieved.

*Pathologist's Report.* The first specimen consisted of a well encapsulated brown-tan 3 by 2 cm encapsulated mass weighing 2 grams. On section this specimen was homogeneous and brown-tan. The second specimen consisted of a 0.5 cm portion of yellow-tan, rubbery firm tissue.

On microscopic examination the large mass revealed numerous small, compact cells with eosinophilic, somewhat granular cytoplasm. Numerous capillaries were seen throughout the mass. In one section adjacent to the capsule a normal rim of parathyroid tissue was seen compressed. The mass was completely encapsulated. The second specimen consisted of a regular appearing parathyroid gland with a normal amount of fat.

## Discussion

The pathologic changes of primary hyperparathyroidism are of five classes: primary hyperplasia, single adenoma, combined adenoma and hyperplasia, multiple adenomas with or without the association of multiple endocrine adenomas, and carcinoma.<sup>2,5,9,11-16</sup> Primary hyperplasia arising *de novo* or from an unknown stimulus is separated into the water-clear cell type described by Albright<sup>11</sup> and the chief cell hyperplasia more recently described by Cope and others.<sup>2,3,6</sup> The

latter has caused much confusion for pathologists because of the similar pathologic appearance of primary chief cell hyperplasia and adenoma. The distinction between these two is, at times, difficult if not impossible when only one gland is examined. Although a functioning adenoma is the most common parathyroid lesion in patients with primary hypoparathyroidism,<sup>9,12,16-19</sup> chief cell hyperplasia with or without association with multiple endocrine adenomas occurs with enough frequency to be of practical importance.<sup>2,9</sup> Chief cell hyperplasia usually involves all parathyroid glands. Therefore, surgical treatment is considerably different than for parathyroid adenoma.<sup>3,20</sup> Because excision of an adenoma results in cure<sup>21,22</sup> and extirpation of anything less than three and one-half glands in primary chief cell hyperplasia will most likely result in continuing or recurrent hyperparathyroidism,<sup>3</sup> it is of utmost importance that the surgeon and pathologist work closely together at the time of the first neck exploration to evaluate all parathyroid glands with biopsy of at least the one other parathyroid than that involved in the lesion.<sup>2</sup> Physical characteristics of the gland—consistency, color and shape and size—are of no appreciable aid in distinguishing between adenoma and chief cell hyperplasia. The microscopic pattern and cytological appearance are frequently very similar in adenomas and chief cell hyperplasia.<sup>14</sup> The presence of a compressed rim of normal appearing parenchyma at the margin of an enlarged gland does give support to a diagnosis of adenoma, but is not a pathognomonic finding as it once was thought to be.<sup>2</sup> Decreased fat content and microscopic nodularity, seen so often in chief cell hyperplasia, can also be of help in the differentiation. If one gland is enlarged and adenomatous, with or without a compressed normal rim of tissue, and the remaining glands are normal or atrophic, adenoma is almost a certainty.<sup>2</sup> Differentiation by this means necessitates exposure of all four glands and biopsy of at least one other gland than the one involved in the lesion, since primary parathyroid hyperplasia usually affects the remaining glands. The possibility of multiple adenomas can be excluded through the careful identification of all glands and biopsy of any suspicious-appearing parathyroids.<sup>14-16,22</sup>

Primary hyperplasia of the clear cell variety is rare. The microscopic and cytological patterns are distinct enough to cause the pathologist no great problems.<sup>9,12,14,23</sup>

The problem of combined adenoma and hyperplasia has recently been studied<sup>5,13,15</sup> and found to be distinguishable from the other causes of parathyroid disease by the procedure just described.

Carcinoma of the parathyroid gland is said to occur in only 3 to 4 percent of all cases of primary hyperparathyroidism.<sup>12,15,24</sup> All parathyroid carcinomas are said to be associated with endocrinologic activity and well marked bone disease,<sup>12,15,24,25</sup> as in Case 1 herein reported. In that case the surgeon suspected the neoplasm was malignant because of the adherence to the recurrent laryngeal nerve. Adherence to surrounding structures is often a helpful clue to malignancy in parathyroid neoplasms.<sup>12,26</sup> It is usually indicative of capsular invasion, which is one of the criteria for diagnosis of parathyroid carcinoma.<sup>9,12</sup> In this respect the criteria for the diagnosis of parathyroid carcinoma parallel those for carcinoma of the thyroid. The neoplasm is so rare that studies of series big enough to permit interpretation of the biological activity of this neoplasm have not been possible. It is thought that the usual spread is first through lymph channels.<sup>12</sup>

Microscopically, parathyroid carcinoma is different from adenoma in a number of ways. As in adenoma, the pattern is variable. Usually, however, capsular invasion is found, although that alone is not sufficient for diagnosis.<sup>9,12</sup> Trabeculation and enlarged atypical mitotic figures are also significant criteria. Mitoses are absent in adenomas and present in carcinomas.<sup>12,24,27</sup> Distinguishing parathyroid carcinomas from atypical adenomas may be extremely difficult. Black and Ackerman<sup>9</sup> restricted the diagnosis of carcinoma to cases in which there is local invasion initially or distal metastasis. We believe that those criteria are too restrictive and that relying entirely on them may give the attending physician a feeling of overconfidence and delay proper treatment. The findings of pronounced cellular pleomorphism, mitotic activity and capsular invasion are more realistic for the diagnosis of parathyroid carcinoma.

## Summary

Two cases of primary hyperparathyroidism (adenoma and carcinoma) were discovered serendipitously in a small community hospital by

Chemistry Panel 12 (Technicon, SMA 12-60) determinations. A discussion of the various types of parathyroid pathology is presented with emphasis on the correlation of gross, surgical and pathologic microscopic findings at the time of the first exploratory operation. Also stressed is the biopsy of more than one gland to differentiate chief cell hyperplasia from adenoma. The gross and microscopic criteria for the diagnosis of parathyroid carcinoma are reviewed.

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# LETTERS *to the Editor*

## Tumor Immunology

*To the Editor:* Dr. I. L. Weissman's editorial comment on tumor immunology (Calif Med 114: 76-78 Mar 1971) is a good review of the field—as far as it goes, which is not far enough. There is, for instance, no mention of Mathé's clinical experience with BCG vaccination in leukemia, or the work of McKhann and others on the re-infusion of autologous lymphoid cells, or Klein's studies on the immunotherapy of skin neoplasms.

In view of the omissions, it is perhaps not surprising that Dr. Weissman concludes: "... there does not appear to be a clinically acceptable method of cancer immunotherapy at this time, and it shall and should remain under laboratory investigation with animal tumors until ...". It should be emphasized that the twin obstacles of immunologic enhancement and graft-versus-host reaction have been circumvented in several clinical studies. Immunotherapy has already begun moving out of the laboratory and into the hospital wards, and has already benefited a small number of cancer victims.

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## The Author Replies

*To the Editor:* Dr. Huemer has transformed my editorial into a review, and as such, has found it lacking: I agree. As a review, it is in-

complete, poorly referenced, and inappropriate. As an editorial concerning tumor immunology as an antigen-specific immune response, I feel it is still appropriate.

In a review I would have critically examined the experiments of Mathé, McKhann, E. Klein, and others. Since Dr. Huemer has brought up these examples as tumor immunotherapy, I shall comment briefly on them.

Mathé (Lancet 1:697, 1969) has published experiments concerned with the use of BCG, a non-specific adjuvant and stimulant of macrophage mitosis and phagocytosis, as an adjunct to chemotherapy in acute leukemias. There is, as yet, no clear evidence that a BCG effect in animal tumors is mediated by a specific immunological response. Furthermore, isolating BCG as a variable in Mathé's data, there is not a statistically significant difference between BCG-treated and control patients ( $X^2=2.21$ ,  $p > .05$ ).

Dr. McKhann, also, has not to my knowledge published any statistically significant data showing the effect of "re-infusion of autologous lymphoid cells" on antigenic malignant neoplasms. He has developed a very perceptive analysis of the tumor-host immunological problem, and has developed an interesting experimental approach, which still requires animal experimentation wherein one can test and control for many of the variables inherent in his experimental model.

I agree with Dr. Huemer that Dr. Edmund Klein has published an interesting approach to therapy of certain skin neoplasms (but not their systemic metastases) and that this phenomenon probably has an immunological basis for its action. I hope that concurrent experimental animal work has been established using this model to elucidate its mechanism of action.

Finally, I remain unconvinced that the twin obstacles of immunological enhancement and GvH reactions have been circumvented in clinical studies in anything but the rare circumstance

(HL-A-matched siblings are required for transplantation of lympho/hematopoietic cells without a fatal GvH as the result).

For all of the above arguments, I feel that although "Immunotherapy has already begun moving out of the laboratory and into the hospital wards," there is great question as to whether it has "already benefited a small number of cancer victims" in a way that will illuminate and encourage further clinical investigation.

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## More Fads, Facts, Fundamentals

*To the Editor:* To add to fads, facts, and fundamentals [Calif Med 112:61, Jun 1970] I should like to suggest two more myths prevalent in medicine.

1. That the degree of excellence of study of a patient is proportional to the number of laboratory tests performed. Chemistry and electrolyte panel, being the order of the day, are repeated at the slightest excuse. Thus the Parkinsonian law of more tests requiring more laboratory equipment and more tests to pay for the equipment becomes operative. As a contributing factor in rising medical costs this probably plays no small part.

2. That everything that happens to a patient taking a drug is *ipso facto* a side effect of the drug. This *post hoc, ergo propter hoc* reasoning in the absence of adequate precedents and lack of physiologic basis has unjustifiably impaired the usefulness of many valuable drugs.

J. J. ROBBINS, M.D.  
*Hayward*

## The Consent to Treatment, in Reverse

*To the Editor:* Responding to an emergency call, Dr. John Doe found himself faced with the following situation. The patient was an unconscious lawyer, who apparently had ingested twenty capsules of Nembutal® prescribed for him the previous day. Attached to the top of his pajamas was the following letter:

Dear Doctor:

As you know, you are not allowed to treat a patient without his consent. In most cases an implied consent is all which is needed. When the patient arrives at the doctor's office or the doctor is called to the patient's bedside, it is implied that the patient agrees to be treated. In surgical cases, the surgeon will ask for a written informed consent to a specific procedure.

In the case of an unconscious patient, it is usually assumed that the patient would give his consent for treatment if his unconsciousness would not prevent him from doing so. In my case such assumption would be erroneous. I am of absolutely sound mind. To prove it, I underwent extensive psychiatric examinations, and attached to this letter you will find a notarized statement from my psychiatrist attesting to my absolutely sound mind and complete mental health. My intention to commit suicide is not caused by any mental disturbance, but by my wish to escape a lingering demise in my desperate physical condition (carcinomatosis of the spine and spinal cord and gangrenous decubital ulcers).

I do not give consent to treatment. On the contrary, I herewith interdict any treatment aimed at my regaining consciousness or prolonging my life. Anyone who might act against my order of refraining from any life prolonging procedures will personally be held responsible for his acts, including financial responsibility, which because of hospitalization for possibly much longer than a year, may run into substantial amounts.

A copy of this letter will be found in my safe-deposit box.

RICHARD ANYONE  
Attorney at Law

How should the doctor act in such a situation?  
What are the legal aspects of the case?

FREDERICK E. EMS, M.D.  
*Petaluma*



# Continuing Education for Physicians

## Traditional Courses vs. Intramural Programs in Community Hospitals

ARTHUR SELZER, M.D., *San Francisco*

THE EXPLOSIVE GROWTH of medical sciences and its application to the practice of medicine produces a challenge to the physician. He is badly in need of guidance to find a reasonable middle course between resistance to progress on the one hand and, on the other, acceptance of every new method of diagnosis and treatment (often oversold by its proponents) as a major advance in medical practice. Such guidance must be provided by effective and well planned continuing education programs. The need for continuing education is self-evident; how to provide it most effectively and how to encourage physicians to avail themselves of it are subjects of current debate. What is the most effective method of keeping the physician up-to-date? Should initiative for updating be left to his own conscience? Should he be pressured by his peers to re-educate himself? Should he be compelled to show evidence that he has kept abreast of current advances?

### Recognition of the Need

It has been pointed out that a license to practice medicine and certification in the specialties are currently awarded for life. Theoretically, a

physician may be engaged in general practice or in specialty practice for 40 years without ever having attended a medical meeting or having read a medical journal. In reality neither is at all likely. The great majority of physicians recognize the need for continuing education, and this is further enhanced by the various review mechanisms of hospital staffs, as well as by the potential legal liability when practicing medicine below the average standard of the community. Nevertheless, serious concern is being shown within as well as without the profession regarding the updating of obsolete knowledge. The American Academy of General Practice was the first professional organization that set up continuing educational requirements for its membership. Currently at least two state medical associations (Pennsylvania and Oregon) are about to introduce compulsory continuing education for their membership. Specialty boards and major specialty colleges are debating means of periodic reassessment of members. Several state legislatures—including California's—are investigating the feasibility of periodic relicensing of physicians.

The California Medical Association has pioneered in showing early interest in the re-education of its membership. More than 20 years ago, the CMA began co-sponsoring, with California's medical schools, postgraduate institutes and "circuit courses." In the early 1960's CMA

The author is chairman of the California Medical Association's Accreditation Committee.

Opinions expressed in this article are those of the author, and do not necessarily represent views of the Accreditation Committee or the Scientific Board.

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co-sponsored teaching institutes at Lake Arrowhead devoted to methodology of medical education, introducing to California physician-teachers the group of medical educators headed by George Miller of Chicago. CMA sponsored two two-day "Planning and Goals Conferences for Continuing Medical Education" (1967 and 1969) with broad representation from the medical profession. As the outgrowth of these conferences, CMA developed a voluntary program of certification of physicians in the state who have completed a prescribed number of units of postgraduate instruction. The program was announced in August 1970. It involves a three-year period from 1969-1972, at the end of which the first certificates will be issued. This program parallels the AMA Recognition Award for participation in continuing medical education; it has many overlaps with the latter, but has slightly higher—though more flexible—requirements.

### Who Sponsors It—and Why?

Part of the difficult problem of postgraduate certification is the development of acceptable standards of continuing medical education. While undergraduate education in medical schools and graduate training programs of internship, residency and fellowship are governed by strictly supervised educational criteria, postgraduate courses have no regulatory mechanisms whatsoever. It has often been stated that continuing medical education is now in a state of disarray comparable to undergraduate medical education at the turn of the century, before the Flexner study. The logical place of origin of continuing medical education is the medical school; yet, until very recently, only a small fraction of schools were engaged in a systematic program of continuing education. Even those that were, frequently assigned lowest priorities—regarding budgets and manpower—to continuing education. Important sources of continuing education were the major professional societies, specialty colleges and professional arms of voluntary health organizations. In addition, hospitals, medical societies, drug manufacturers—even travel agencies—sponsor courses for physicians. Motivation behind sponsorship of postgraduate courses varies widely: some genuinely desire to provide needed service to the profession; others consider it a matter of prestige and a means for

institutional publicity; still others wish to promote a drug or a method of therapy, or even use it as a means of recruitment for an overseas trip.

### Deficits in Methodology

During the past two decades great advances have been made in the methodology of education. Be it kindergarten or a graduate school of a major university, educators concentrated upon effective ways of channeling given information to the learner. Various ways of measuring the learning process were used to evaluate effective teaching. Yet in the medical field the acceptance of newer concepts in education was very slow at all levels, but particularly at the postgraduate level. Even today, little attention is paid to the *method* of education; all the concentration is upon the *content*.

It is automatically assumed that an expert in a given field is the best person to teach the subject within his field. The great majority of postgraduate courses use the traditional formula, that is, to invite a group of "expert" lecturers from far away (as many as the budget will permit), to add a few local speakers and to arrange a series of lectures for a large group of students. The learning experience in such courses is purely passive. It takes an unusually gifted teacher to be able to provide information in such a way that the listener can improve his comprehension of a disease and apply new knowledge in his practice. Lecturers are often entertaining. The listener may enjoy the lectures in the way he would enjoy a movie or a show; he may remember some stories, but he receives little factual medical information. Some of the well-known postgraduate courses are in reality a thinly disguised means of soliciting a monograph on a given subject. The course consists of a large number of presentations by all the known experts in a certain field—a parade of "stars," each of whom is given a ridiculously short time (ten to fifteen minutes) to summarize his contribution; however, he obligates himself to submit a manuscript for the monograph. From the education standpoint, one might think of such a meeting as a caricature of a postgraduate course.

Are postgraduate courses for large audiences outdated? Not necessarily. A properly organized series of lectures may become a valuable learning experience in spite of the fact that it constitutes a passive experience for the student.



If all instructors are able to define a specific objective in their presentations, if they are able to concentrate on a finite number of points they wish the student to learn, if the course has a "master plan" tying the various presentations together, and if the instructors are selected because of their demonstrated ability as *teachers*—not merely experts in a field—then a subject can be handled in this manner with benefit to the audience. However, preference should be given to teaching experiences with active involvement of the learner. This may be a preceptorship or a short-term residency-like experience, small group instruction, discussion groups, seminars, workshops, and the like.

### The Community Hospital as a Logical Setting

The most logical place for the physician to be exposed to continuing education is the setting of the hospital in which he treats his patients. A properly organized continuing education program in the community hospital aimed at its own staff has many advantages over formal postgraduate courses. A staff member can relate new advances to his own patients or to cases he is familiar with and can do so without travelling to a "medical Mecca." Stimulated by discussions at the Planning and Goals Conferences and their recommendations, the Accreditation Committee recently created by CMA has decided to concentrate upon the community hospital. The Committee considered the community hospital as a potential place in which an "educational atmosphere" could be developed, providing a means of helping the entire staff with difficult medical problems. The Committee developed 11 standards, which will be considered as the basis for extending category A credit toward the CMA certificates.

### Standards

These standards include certain physical facilities for conducting teaching activities: meeting rooms, classrooms, auditoriums or other designated areas which could be equipped with picture projection facilities, television viewers, sound amplification and other necessary audiovisual aids. Library facilities with access to current medical journals and a reasonable number of reference books should be available to the

staff, preferably but not necessarily on the premises. The hospital staff should have a standing education committee that is directly involved in the planning of continuing education. Leadership should be provided by a specific staff member, not necessarily a full-time director of medical education, but a person with reasonable familiarity with modern educational methods. Teaching sessions, weekly or monthly rounds, conferences, lectures, seminars, workshops, should be well planned in advance. Preferably a curriculum should be followed which would allow a balanced presentation of the principal fields of medicine or the respective specialties over a period of time—for example, one to three years. The objective of each teaching session should be kept in mind: Is it primarily aimed at the general practitioner, the specialist, the subspecialist? A realistic attendance record should be kept on file, so that those claiming credit for a session can demonstrate that they have attended the meeting.

Three standards are considered by the Accreditation Committee to be of crucial importance: the determination of needs, the process of evaluation, and the coordination with other programs. The first two require true involvement and cooperation of the majority of the hospital staff. By determination of needs is meant that a method should be designed to find out points of weakness in the practice in a given institution. Means are available by which a hospital can compare its records with those of the general average practice in other hospitals. This can be done by chart audits, by mortality conferences, by tumor boards, by review of statistics regarding the length of stay in the hospital, the ratios of various kinds of operations to the total number and the mortality rates associated with each, the usage of certain drugs, and the like. The process of evaluation deals with collection of evidence that teaching has actually led to improvement in the care of patients as a result of continuing education. Direct evaluation—by means of post-testing—is less important than collection of indirect evidence, again by means of audits and review of various statistics, whereby the results of changed modes of practice can be detected. Finally, the Committee will encourage the utilization of all the resources in the area in a coordinated manner: smaller communities with two or three hospitals should pool their facilities

into joint teaching sessions; various facilities provided by Regional Medical Programs should be given wide distribution, with an effort to avoid duplication.

## Implementation

A question frequently asked is: can a hospital in a smaller community fulfill the criteria and receive full accreditation? The answer is that virtually any hospital, given the proper motivation of its staff, could develop accreditable teaching programs. In order to facilitate the development of new programs, the Accreditation Committee has recommended to the Scientific Board of the CMA the sponsorship of postgraduate institutes devoted to educational methods, to which all hospitals interested in developing educational programs will be able to send representatives—future leaders in continuing education.

Many hospitals already maintain education programs. Most follow the traditional pattern of periodically inviting lecturers from nearby medical schools, or subscribing to closed-circuit television programs or television tapes, or partaking in radio panels. Such programs appear to be inferior to those that would be initiated at the hospital. The inherent weakness of lectures has already been commented upon. Televised clinics *per se*, as passive exercises, are seldom effective, although as a nucleus around which an organized workshop is conducted they may be a most valuable teaching tool. In general, an "expert" from a teaching institution could often be better utilized as a discussant at live clinics—as a panelist rather than as a lecturer. With ingenuity, the educational leader of the hospital can organize good teaching sessions with minimal resources. He may discover teaching talent within his own staff, and if he did he could organize live clinics with local resources. He may take advantage of large libraries of teaching films and tapes from the audiovisual branch of the National Library of Medicine or from other sources, organizing teaching sessions around such films.

## Need for Quality Control

The problem of continuing education is a complex one. Almost every physician recognizes the need to keep abreast of recent advances in the science and practice of medicine. Each may find his own most effective way to fulfill this need. Medical journals provide one mode of learning; as a rule, original papers are less valuable for this purpose (they require training in critical evaluation of the evidence) than review articles and journals of postgraduate nature. Audio tapes provide another method of self-instruction. Annual meetings of medical societies, specialty associations, colleges and academies provide another large forum for updating. Except for societies specifically devoted to research, most such meetings provide a mixture of original communications and review papers or panels, providing postgraduate education. Finally, there are "courses." The number of formal postgraduate courses is enormous. The physician's daily mail contains brochure after brochure advertising courses on any imaginable medical and non-medical subject. No accreditation process can ever provide information as to which of the courses may be of a real educational benefit. In contrast to undergraduate and graduate medical education, where there is a finite curriculum, a measurable objective and an endpoint to the studies, continuing education has no time limit, no easily measurable standards; it has no quality control other than the institution behind it. Accreditation of postgraduate institutions can at best set a minimum standard for planning and preparation of courses; it cannot assure the value of individual courses. Therefore, it would appear that the development of a "learning atmosphere" in the physician's own hospital, with a continuous, planned, well reviewed educational program centered around practice in that hospital may be the best solution to the difficult problem. If such programs can be successfully conducted in many hospitals, the time may come that they would deserve preferential treatment in the various certification programs.



## Information

### Methadone Maintenance Techniques

The California Medical Association's Committee on Dangerous Drugs believes that the AMA statement on methadone deserves dissemination in CALIFORNIA MEDICINE, as representing a mature and restrained analysis of a current situation in keeping with a House of Delegates resolution to promote an educational program.

It reiterates the fact that restraint should be used and records kept. The major point, essentially, is that it should not be available for emotionally unstable people who have not been on heroin but who feel that it would be interesting to be on methadone. It is a good substitution treatment for heroin addicts but should not itself become a way of life.

Used under appropriate circumstances methadone may represent one of the most constructive approaches to the problem to date.

WILLIAM F. QUINN, M.D.  
*Chairman*  
*Committee on Dangerous Drugs*

*Combined Statement of the Council on Mental Health and its Committee on Alcoholism and Drug Dependence, American Medical Association, and the Committee on Problems of Drug Dependence, National Research Council*

Over the years, since its inauguration by Dole and Nyswander in 1964, the concept of "methadone maintenance" has come to mean many things. Each mode of oral methadone used in a maintenance program, however, would still seem to be oriented primarily toward social rehabilitation and toward voluntary participation by the patient. Some aspects of the program have been clearly established; others are still on a research basis.

In its 18th report, the World Health Organization Expert Committee on Drug Dependence stated: "Methadone maintenance (in the pharmacological sense) is the continuing daily oral administration of methadone under adequate

medical supervision, the dose being adjusted, a) to prevent the occurrence of abstinence phenomena, b) to suppress partially or completely any continuous preoccupation with the taking of drugs of the morphine type, and c) to establish a sufficient degree of tolerance and cross-tolerance to blunt or suppress the acute effects of such agents."<sup>1</sup>

Some modalities include the indeterminate administration of methadone, perhaps for life, while others include a therapeutic goal of attaining drug abstinence at some appropriate time.

There are differences in dose levels of methadone administration. Some programs are based on high doses to attain high tolerance levels while other programs utilize moderate or small dose levels. Most programs incorporate a variety of allied services such as general medical evaluation and care, psychiatric services, and a host of different social rehabilitative techniques in varying combinations and ranging from minimal levels of attention to all-encompassing care. A few programs are beginning to study a modality of simply providing methadone without any of the allied services.

Other variables that exist from program to program include differing criteria for patient selection, as well as differences in age, sex, drug history, history of criminal activity, employment record, education level, family structure and general medical and psychiatric status.

In view of these considerations, the American Medical Association and the National Research Council make the following recommendations:<sup>2</sup>

1. Methadone maintenance programs should include at least the following elements in order to constitute proper medical practice:
  - a. adequate facilities for the supervised collection of urine and for frequent and accurate urine testing for the presence of morphine and other drugs,
  - b. general medical and psychiatric services,
  - c. hospital facilities as needed,
  - d. adequate staff,
  - e. rigid controls of methods of dispensing methadone to prevent diversion to illicit sale or to possible intravenous use.

<sup>1</sup>World Health Organization Technical Report Series (1971) No. 460, P. 22.

<sup>2</sup>These recommendations are in essential agreement with the recommendations made by the Methadone Maintenance Evaluation Committee of New York, as enunciated in that Committee's report to the Third National Conference on Methadone Treatment in New York, November 4, 1970.

2. Care should be exercised in the selection of patients to prevent the possibility of causing the person who has not been dependent on heroin to become dependent on methadone.
3. There should be continued evaluation of the long-term effectiveness of methadone programs for persons who are stabilized on an inpatient or an ambulatory outpatient basis.
4. Where feasible, staff members of new methadone maintenance programs should be trained in this technique in an established effective program.
5. Continuing research is essential particularly with reference to:
  - a. the use of properly trained practicing physicians as an extension of organized methadone maintenance programs in the management of those patients whose needs for allied services are minimal. These patients should remain in contact with the methadone maintenance program for periodic evaluation, including urine testing.
  - b. the role of methadone maintenance in the treatment of heroin dependent patients under age 18 years.
  - c. the use of methadone maintenance in combination with other approaches to the treatment of morphine type dependence.

Methadone maintenance is not feasible in the office practice of private physicians. The individual physician cannot provide all of the services for the various therapeutic needs of the patient. The individual physician also is not in a position to assure control against redistribution of the drug into illicit channels, to maintain control of doses, or to establish the elements for proper evaluation of the treatment. Practicing physicians, however, should cooperate with methadone maintenance programs in their communities and offer whatever services they may be capable of providing.

## Highlights of Auscultation In Congenital Heart Disease

### Part II

JOSEPH K. PERLOFF, M.D.

*Material Supplied by the American  
Heart Association*

*The Pulmonary Orifice.* The midsystolic murmur of isolated congenital valvular pulmonic stenosis is typically loudest in the second left intercostal space and radiates upward and to the left. The length of the murmur varies directly with the degree of obstruction so that in mild pulmonic stenosis the murmur ends before both components of the second heart sound, whereas in severe pulmonic stenosis the murmur goes through aortic closure but necessarily ends before the delayed soft or inaudible sound of pulmonary valve closure. The murmur is introduced by a pulmonic ejection sound which often distinctively waxes with expiration and wanes with inspiration. Severe obstruction is associated with powerful right atrial contraction which distends the right ventricle in presystole and in so doing generates an atrial or fourth heart sound. Specific attention should be called to the systolic murmur that accompanies stenosis of the pulmonary artery and its branches, a congenital malformation that often follows maternal rubella. These murmurs are widely distributed in the right chest, axilla, and back, and must be sought by auscultation at non-precordial sites during quiet respiration.

When one speaks of pulmonary regurgitation, the high frequency blowing Graham Steell mur-

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Part II of a two-part article. Part I appeared in the May issue.

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mur comes to mind. However, pulmonary regurgitation may occur without pulmonary hypertension when there is a congenital or acquired anatomic defect of the valve itself, and this murmur differs from that of Graham Steell. The murmur begins at an interval after the second heart sound, is crescendo-decrescendo in shape, ends well before the next first heart sound, and is low to medium pitched since a low diastolic pressure in the pulmonary trunk results in a low rate of regurgitant flow.

*The Atrial Septum.* Atrial septal defect can be one of the most readily diagnosed congenital anomalies of the heart although from an auscultatory point of view, the malformation is often overlooked because of the relatively inconspicuous murmur. It should be borne in mind that the *defect itself* is acoustically silent and the shunt is diastolic; when the right ventricle ejects the large stroke volume accumulated in diastole, a relatively short grade 2-3 pulmonic systolic murmur is generated. The right ventricle takes longer to expel its large stroke volume so the second component of the second heart sound (pulmonary closure) is delayed; furthermore, the physiology of the circulation in atrial septal defect results in *fixed* splitting of the second heart sound which means that the split remains unchanged during respiration.

The soft murmur of atrial septal defect may be mistaken for an innocent systolic murmur, especially in children. However, the usual innocent murmur is a vibratory, buzzing, pure to medium frequency event that is best heard along the lower sternal edge and toward the apex and is accompanied by *normal* splitting of the second heart sound. In addition, *complete right bundle branch block* is associated with *wide* splitting of the second heart sound but usually not with *fixed* splitting and hence can be distinguished from the wide fixed splitting of the atrial septal defect.

*The Ventricular Septum.* The typical holosystolic left sternal edge murmur of ventricular septal defect is well known. Progressive pulmonary hypertension decreases the left to right shunt and shortens the murmur; when the shunt is reversed (Eisenmenger's Complex), the murmur through the defect is abolished. It is important to recognize that an early systolic murmur can *also* occur with *very small* nonpulmonary hypertensive ventricular septal defect in which the shunt is interrupted in latter systole. Such murmurs are soft,

pure, high frequency, and quite localized at the mid to lower left sternal edge; as time goes on these murmurs may disappear because of spontaneous closure of the defect.

Fallot's tetralogy—the commonest cyanotic congenital cardiac above age 4 years—has been taken to represent a large ventricular septal defect upon which varying degrees of pulmonic stenosis are imposed. Progressive right ventricular outflow obstruction decreases the left to right interventricular shunt and shortens and finally abolishes the holosystolic murmur leaving an isolated midsystolic murmur of pulmonic stenosis. As obstruction increases further, right ventricular blood is shunted through the ventricular septal defect into the aorta; accordingly, pulmonary flow decreases, cyanosis increases, and the pulmonic stenotic murmur progressively shortens and softens disappearing completely with pulmonary atresia.

*The Great Vessels.* When an uncomplicated patent ductus arteriosus joins the great vessels, a characteristic continuous machinery murmur peaks around the second heart sound and is maximal at the left base. Several words of caution are appropriate. Occasionally a loud venous hum in young children transmits below the clavicles and is mistaken for a patent ductus arteriosus; this error can be avoided by compressing the deep jugular veins, a maneuver that abolishes the hum. In large patent ductus, progressive pulmonary hypertension decreases the left to right shunt so that the continuous murmur shortens, then becomes systolic, and when the shunt is reversed, disappears entirely. At this point, the recognition of patent ductus does not depend upon auscultation; instead, the presence of differential cyanosis (blue toes and pink fingers) makes the diagnosis.

### *The Myocardium*

*Hypertrophy.* Increased force of atrial contraction usually distends a hypertrophied ventricle in presystole. Atrial or fourth heart sounds accompany the presystolic distention and are useful signs of hypertrophy such as in aortic stenosis or systemic hypertension on the left side and pulmonic stenosis or pulmonary hypertension on the right. In the pulmonary hypertension of emphysema, the atrial sound is often heard in the epigastrium since all of the heart sounds—including a loud pulmonary closure sound—are damped because of the large anteroposterior chest dimensions.

*Failure.* Third heart sounds are physiologic in children and young adults but pathologic in older subjects. Ventricular failure is a common cause of abnormal third heart sounds and should be specifically sought with light touch of the stethoscopic bell in all patients in whom heart failure is suspected. It is a point of interest that the effect of cardiac infarction on the left ventricular myocardium commonly results in the need for an increased distending force that is provided by augmented atrial contraction; atrial or fourth heart sounds are prevalent in this context.

An ischemic left ventricle may take longer than normal to eject so aortic valve closure may fall *after* pulmonary closure causing reversed or paradoxical splitting of the second heart sound. The commoner cause of paradoxical splitting however

is left bundle branch block or a right ventricular pacemaker which is its electrical equivalent.

*Constriction.* Myocardial constriction—as in constrictive pericarditis—results in high atrial pressures and rapid flow into nondistensible ventricles. Under these circumstances, loud early third heart sounds occur and have been called “early diastolic sounds” of constrictive pericarditis. Similar sounds occur in the restrictive form of primary myocardial disease.

*Summary.* Modern instrumentation has not eclipsed the need for sophisticated auscultation. On the contrary, clinical research has gone far in clarifying the meaning of auscultatory events in acquired and congenital heart disease and has increased the value of the stethoscope as a clinical tool.

#### HOME TESTS FOR DEAFNESS MAY BE TOO LOUD

“Typically the parent of a deaf child senses that something is wrong in the first year of life. Then when speech would normally begin but doesn’t, suspicions increase. . . . Parents will quite often bang pots together behind the child or take a hammer and hit a frying pan. Frequently, the resultant sounds are so loud or the vibrations are so great that even the child with a profound hearing loss jumps. The child may be responding to the vibrations or to the sound; but remember that a child is educationally and socially deaf when he is unable to hear speech sounds well enough to understand them. It is this kind of a hearing loss which must be diagnosed. The child may be able to hear airplanes, trucks, and banging pots and pans; but if he can’t understand speech sounds, for practical purposes he’s deaf. By these criteria of deafness, home tests obviously miss a great deal of deafness.”

—McCAY VERNON, PH.D., Chicago

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 14, in the Audio-Digest Foundation’s subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# Physician Fee Indices in California and the U.S.

## Recent Data and Long-Term Trends

A Socio-Economic Report of the Bureau of Research and Planning,  
California Medical Association

ACCORDING TO DATA compiled by the Bureau of Research and Planning, physicians' fees in California increased 4.4 percent in the first half of 1970. For the same period, the U.S. Bureau of Labor Statistics reported increases of 4.6 percent nationally, 5.7 percent in the Los Angeles-Long Beach Metropolitan Area, and 5.3 percent in the San Francisco-Oakland Metropolitan Area.

Among the four basic categories of procedures for which the California data are collected, fees for medical procedures (visits, consultations, etc.) showed the most rapid rate of change, with an increase of 5.1 percent, while laboratory services showed the slowest rate of change, with an increase of 3.2 percent during the period.

### *Some Background about the California Physician Fee Index*

The California Physician Fee Index has been compiled by the Bureau of Research and Planning of the California Medical Association since mid-1962. Since that time, there have been two changes in the 26 individual procedures for which usual fee data are gathered and seven separate random samples of physicians have provided the necessary information.<sup>1</sup> The data have provided complete and reliable statistics on statewide trends in physicians' fees and have made possible comparisons with national patterns which other-

wise could not have been made. This *Socio-Economic Report* contains recent results and some detailed longer-term comparisons.

### *Long-Term Trends Reveal Patterns in Fee Changes*

A total of 17 procedures which physicians perform have been surveyed in *every* period between June 1962 and June 1970. Indices for each of these procedures, individually, are listed by 1964 California *Relative Value Studies* (RVS) procedure code number in Table 1. This table also contains information for the total index<sup>2</sup> and for each of the four separate sections of the RVS. These aggregate figures are based not only on the procedures shown individually in the table, but rather on all appropriate procedures surveyed during the course of the study. Although the procedures surveyed represent only a small proportion of the total number of procedures performed by a physician, they include those that are performed most frequently and, consequently, represent a sizable proportion of the total expenditures for physician's services.

In the eight years since this study was originated, fees in the *Surgery* section have increased 49.7 percent, the greatest rate among the four RVS sections. Fees for procedures in the *Medicine* section have risen almost as fast, with an increase

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco, Ca. 94102.

<sup>1</sup>See *Socio-Economic Report* Vol. X, No. 4, April 1970, for detailed information about survey methodology.

<sup>2</sup>Recent changes in the total index will be discussed at length in connection with Table 2.

TABLE 1.—California Physician Fee Index for All Items, by RVS Section, and for Individual Procedures:  
Semi-Annual Figures for June 1962 to June 1970

1964 CMA-RVS Code number*	1962		1963		1964		1965		1966		1967		1968		1969		1970	
	June	Dec	June	Dec	June	Dec	June	Dec	June	Dec	June	Dec	June	Dec	June	Dec	June	Dec
All items .....	100.0	101.6	103.9	105.8	107.4	108.8	110.8	112.5	116.1	119.1	121.4	123.9	126.6	129.1	132.3	136.3	142.3	
RVS Section																		
Surgery .....	100.0	101.6	104.2	106.5	108.1	109.5	111.7	114.4	118.2	121.7	124.6	128.2	131.8	134.6	138.4	143.6	149.7	
Radiology .....	100.0	101.6	102.1	103.0	104.2	104.1	105.1	105.6	107.1	108.7	110.4	111.8	113.5	114.5	115.4	117.6	122.6	
Laboratory .....	100.0	101.2	102.5	102.3	103.0	103.7	105.0	105.4	107.6	109.5	110.6	112.4	113.9	114.9	117.6	119.6	123.4	
Medicine .....	100.0	101.7	102.6	103.7	105.1	106.8	108.9	110.7	115.6	118.8	121.2	123.4	126.1	129.6	133.7	137.8	144.8	
Individual procedures																		
2111 .....	100.0	104.4	106.2	100.8	103.3	102.8	104.5	108.2	116.1	117.5	125.1	126.1	127.0	129.2	131.1	136.1	139.2	
2992 .....	100.0	102.2	103.9	106.9	107.7	109.4	110.6	111.5	115.5	119.3	121.9	123.4	125.9	127.8	130.6	134.2	141.1	
3261 .....	100.0	100.9	102.8	106.2	108.0	108.4	111.4	111.7	115.4	120.0	121.4	123.7	126.4	130.2	135.4	140.0	144.3	
3380 .....	100.0	100.9	103.6	104.0	105.6	106.7	107.6	111.1	114.8	121.8	125.1	126.2	128.9	130.7	133.6	137.7	144.9	
3631 .....	100.0	101.3	105.1	106.0	107.9	110.7	112.3	114.2	117.1	123.7	125.6	128.1	130.0	134.1	136.9	140.9	150.7	
3930 .....	100.0	98.9	101.1	101.2	101.9	105.1	107.0	105.2	111.4	112.8	112.8	113.3	116.0	116.7	119.6	121.7	129.5	
4614 <sup>1)</sup> .....	100.0	102.8	106.1	107.9	109.5	111.0	113.2	114.3	115.1	118.4	121.8	123.3	126.5	128.6	132.6	137.6	144.5	
4821 .....	100.0	102.2	102.6	104.1	105.4	107.6	108.8	111.9	112.9	115.6	118.4	120.6	124.9	127.5	130.7	136.6	143.4	
7100 .....	100.0	102.4	103.7	101.8	104.2	105.1	106.7	106.9	108.4	111.4	113.3	115.0	116.1	117.3	118.8	121.2	125.5	
8628 .....	100.0	100.5	101.4	100.8	101.7	102.1	103.0	102.1	103.2	103.6	104.6	106.9	108.3	109.0	110.9	112.0	115.3	
8936 <sup>2)</sup> .....	100.0	100.7	104.1	104.8	105.9	107.0	109.2	107.2	108.3	110.6	111.7	114.6	116.1	116.5	119.5	122.1	125.9	
9004 .....	100.0	100.9	101.5	101.5	102.8	104.3	106.2	110.2	115.5	118.6	121.2	123.4	125.9	129.4	133.6	137.4	144.6	
9014 .....	100.0	102.3	105.3	105.9	108.0	109.7	112.4	113.5	118.7	123.6	126.3	130.1	134.5	138.7	143.0	148.6	154.7	
9024 <sup>3)</sup> .....	100.0	102.5	103.6	106.1	108.2	110.1	112.1	113.8	117.0	120.9	121.9	124.0	127.2	130.5	134.1	139.6	145.1	
9028 <sup>4)</sup> .....	100.0	101.3	102.5	103.9	104.8	107.5	110.7	114.5	116.7	123.7	126.9	128.8	132.5	135.2	140.7	145.6	152.1	
9030 <sup>5)</sup> .....	100.0	102.3	104.6	98.9	100.8	101.4	103.6	106.7	109.5	114.4	116.2	118.3	119.9	121.7	125.6	129.4	135.4	
9101 <sup>6)</sup> .....	100.0	102.0	102.5	101.7	102.4	103.1	103.7	104.7	106.7	108.2	109.3	110.2	111.7	113.2	116.3	118.5	122.5	

\* See Appendix for list of procedures.

<sup>1)</sup> #4617 in 1960 RVS. <sup>2)</sup> #8934 in 1960 RVS. <sup>3)</sup> #9023 in 1960 RVS. <sup>4)</sup> #9026 in 1960 RVS. <sup>5)</sup> #9028 in 1960 RVS.

<sup>6)</sup> Electrocardiogram is considered as a laboratory procedure for purposes of the Index.



of 44.8 percent. *Radiology* and *Laboratory* fees have increased at a much slower rate of 22.6 percent and 23.4 percent, respectively.

#### *Fees for Visits, Consultations Show Rapid Increase*

During the first half of 1970, fees for physician visits and consultations rose 5.1 percent.<sup>3</sup> This increase was considerably higher than the 3.1 percent increase in fees for these procedures reported during the last six months of 1969, and is illustrative of the recent upswing of the entire index. A major contributing factor to this rapid increase was the 5.2 percent change in fees for office visits.

#### *Identical Increases in Radiology and Surgery*

Fees for radiology and surgery procedures increased 4.2 percent between December 1969 and June 1970. This is a particularly high increase for radiology which, since the index was started, has had the slowest overall rate of increase of the four RVS sections. Also, this increase is higher than the fee changes in surgery (3.8 percent) or in radiology (1.9 percent) reported for the last half of 1969. Of the eight surgical procedures studied since the inception of the index, fees for herniorrhaphy have shown the highest long-term increase (50.7 percent) as well as the sharpest increase in early 1970 (7.0 percent). The only radiology procedure that has been surveyed constantly since 1962 is the diagnostic, single view chest x-ray, which has shown an increase of 25.5 percent.

#### *Laboratory Services Show Smallest Increase*

In the six-month period between December 1969 and June 1970, the average fees for laboratory services increased at a slower rate (3.2 percent) than did other types of services, but at a much faster rate than the 1.7 percent increase exhibited in the previous six-month period. Of the two procedures included in the laboratory component that have been surveyed continuously for the last eight years, the fee for a urinalysis has increased considerably more rapidly (25.9 percent) than has the fee for a complete blood count (15.3 percent).

#### *Early 1970 Figures Show Marked Fee Increases*

The California Physician Fee Index shows a statewide increase of 4.4 percent in the first half of 1970, only slightly lower than the nationwide

increase of 4.6 percent reported by the U.S. Bureau of Labor Statistics for the period.<sup>4,5</sup> As can be seen in Table 2, increases of such magnitude are especially significant when viewed in the context of their considerably slower rates of change (3.0 percent and 2.9 percent, respectively) in the last six months of 1969. These figures realize a trend predicted by the BLS and reported in an earlier Socio-Economic Report (April 1970) that the rate of inflation experienced in the latter half of 1969 would not decline and could increase during 1970. Although a slowdown is now predicted in the general level of prices, items in the service sector, such as physicians' fees, may not be affected. According to an article in *The Wall Street Journal* (July 22, 1970)

... the government is presently hopeful that restraint in wage demands will create an economic slowdown in the latter half of 1970, but services, such as medical care, are not affected by such restraints. The Labor Department reported that services accounted for about half of the increase of the (total) Consumer Price Index in the month of June.

#### *BLS Indicates Rapid Increases in Metropolitan Areas*

In addition to national figures, the Bureau of Labor Statistics (BLS) has reported that in the first half of 1970 physicians' fees increased at rates of 5.7 percent in the Los Angeles-Long Beach Metropolitan Area and 5.3 percent in the San Francisco-Oakland Metropolitan Area. For the Los Angeles area, this is a continuation of the trend started in the last six months of 1969 when physicians' fees increased 5.8 percent. For the San Francisco area, this 5.3 percent change is exceptionally high; it compares with a 3.4 percent increase in the last six months of 1969. It is interesting to note, however, that figures for the second quarter in both cities suggest a decline in the rate of increase.

Specific types of metropolitan area indices, such as that for physicians' fees, were first published

<sup>3</sup>Tables 1 and 3 do not show percent changes as such. These figures are calculated by dividing the difference in the index between time 1 and time 2 by the index for time 1.

<sup>4</sup>It should be noted that the two indices are not exactly comparable, since different procedures are included in each. However, general comparisons, particularly in terms of long-term trends, can be made. The CMA index, briefly described, is based on usual fee information for 26 individual procedures supplied via a mailed questionnaire by a sample of some 450 physicians throughout the State. The BLS index is based on seven procedures, including four types of physician visits and three surgical procedures. The size of the sample of physicians used, each of whom is personally contacted for each survey period, is not divulged by the Bureau; suffice it to say that the statistical validity of their index is seldom, if ever, questioned. Nevertheless, the relatively small size of the samples of physicians included in each individual area may subject these regional indices to more fluctuation than is optimal in such measurements.

<sup>5</sup>The Consumer Price Index, U.S. City Average and Selected Areas. U.S. Department of Labor, Bureau of Labor Statistics. Monthly issues contain tabular information for selected items and groups.

**TABLE 2.—Physician Fee Index and Percentage Increases for the United States, San Francisco, Los Angeles and California: Quarterly Figures from December 1964-June 1970 (December 1964=100.0)**

Month and Year	United States <sup>1</sup>		San Francisco <sup>1</sup>		Los Angeles <sup>1</sup>		California <sup>2</sup>	
	Index	Percent change	Index	Percent change	Index	Percent change	Index	Percent change
1964								
December	100.0	—	100.0	—	100.0	—	100.0	—
1965								
March	3)	—	101.1	1.1	101.2	1.2	101.0	1.0
June	101.9	1.9	101.6	0.5	101.4	0.2	101.8	0.8
September	3)	—	101.9	0.3	101.6	0.2	102.6	0.8
December	103.8	1.9	103.2	1.3	101.6	0.0	103.3	0.7
1966								
March	105.6	1.7	105.2	1.9	102.5	0.8	3)	—
June	107.7	2.0	107.4	2.1	103.5	1.0	106.6	3.2
September	110.1	2.2	110.4	2.8	105.5	1.9	3)	—
December	111.9	1.6	111.4	0.9	108.9	3.2	109.4	2.6
1967								
March	114.1	2.0	112.3	0.8	111.6	2.5	3)	—
June	115.6	1.3	113.7	1.2	113.3	1.5	111.5	1.9
September	117.3	1.5	114.5	0.7	113.7	0.4	3)	—
December	118.7	1.2	115.4	0.8	114.6	0.8	113.8	2.1
1968								
March	120.5	1.5	117.5	1.8	116.0	1.2	3)	—
June	122.0	1.2	118.1	0.5	117.2	1.0	116.3	2.2
September	124.9	2.4	118.7	0.5	117.9	0.6	3)	—
December	127.0	1.7	119.4	0.6	120.5	2.2	118.6	2.0
1969								
March	129.9	2.3	119.9	0.4	123.5	2.5	3)	—
June	132.4	1.9	120.9	0.8	125.0	1.2	121.5	2.4
September	134.5	1.6	123.0	1.7	126.4	1.1	3)	—
December	136.2	1.3	125.0	1.6	132.3	4.7	125.2	3.0
1970								
March	139.4	2.3	129.1	3.3	137.8	4.2	3)	—
June	142.4	2.2	131.6	1.9	139.8	1.4	130.7	4.4

<sup>1</sup>U.S. Department of Labor, Bureau of Labor Statistics

<sup>2</sup>Bureau of Research and Planning, California Medical Association

<sup>3</sup>Data not compiled

by the BLS in December 1964. Since that time, fees in Los Angeles have increased 39.8 percent, about eight points above the 31.6 percent change in San Francisco physicians' fees for the same 66-month period. The 42.4 percent increase recorded nationally exceeds the rate in either of these metropolitan areas. However, in the 12-month period from June 1969 to June 1970, the national index and the California index both increased 7.6 percent while the indices for San Francisco and Los Angeles showed much higher increases of 8.9 percent and 11.8 percent, respectively.

#### *Fee Changes for Individual Procedures Compared*

The Bureau of Labor Statistics and the Bureau of Research and Planning collect data on several of the same individual procedures. This allows

certain comparisons of physicians' fees on the state and national level, as shown in Table 3.

Fee data for home and office visits, tonsillectomy and adenoidectomy, and obstetrical care have been collected by both agencies since 1962; data for herniorrhaphy have been collected since 1963; and data for cholecystectomy, prostatectomy, and fracture reduction have been collected since 1965. Fee indices for each of these procedures are shown in the table for both California and the total U.S.

#### *Recent Increases Generally Greater Nationally*

The first six months of 1970 showed that fees for both home and office visits rose faster nationally than in California. The former rose 5.4 percent in the U.S., compared with 4.1 percent in the state; the latter showed a 5.8 percent increase na-



TABLE 3.—A Comparison of Selected Procedures in the Physician Fee Index, in California and in the U.S.: Semi-annual Figures since June 1962

Period	General physician house visit <sup>1</sup>		General physician office visit <sup>1</sup>		Cholecystectomy <sup>2</sup>		Prostatectomy <sup>2</sup>		Fracture <sup>2</sup>		Herniorrhaphy <sup>3</sup>		Tonsillectomy and Adenoidectomy <sup>4</sup>		Obstetrical care <sup>1</sup>	
	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.	Calif.	U.S.
1962																
June	100.0	100.0	100.0	100.0									100.0	100.0	100.0	100.0
December	102.3	101.0	100.9	101.1									102.2	101.0	102.2	100.7
1963																
June	105.3	102.1	101.5	102.4									103.9	102.2	102.6	101.6
December	105.9	102.8	101.5	103.2							100.0	100.0	106.9	104.0	104.1	102.2
1964																
June	108.0	104.7	102.8	104.6							101.8	100.8	107.7	105.4	105.4	104.3
December	109.7	107.0	104.3	106.2							104.4	102.5	109.4	107.0	107.6	105.3
1965																
June	112.4	109.0	106.2	108.7							105.9	103.2	110.6	108.4	108.8	106.2
December	113.5	111.9	110.2	110.7	100.0	100.0	100.0	100.0	100.0	100.0	107.7	105.7	111.5	109.7	111.9	107.0
1966																
June	118.7	117.0	115.5	115.2	104.2	101.4	104.0	102.5	104.3	101.2	110.4	107.5	115.5	113.2	112.9	110.1
December	123.6	121.4	118.6	119.9	107.2	102.5	105.2	106.9	106.9	103.5	116.6	110.5	119.3	116.3	115.6	115.2
1967																
June	126.3	124.8	121.2	124.6	109.0	106.0	110.6	109.4	109.2	107.7	118.3	114.1	121.9	118.0	118.4	119.8
December	130.1	127.9	123.4	128.3	110.5	109.9	111.1	114.3	111.5	111.3	120.7	116.0	123.4	122.1	120.6	121.7
1968																
June	134.5	133.0	125.9	131.6	111.5	113.0	113.1	116.6	113.7	116.2	122.5	119.3	125.9	124.9	122.7	125.1
December	138.7	137.8	129.4	135.3	113.5	115.7	115.8	121.2	115.8	119.6	126.3	121.2	127.8	129.1	125.3	129.2
1969																
June	143.0	143.4	133.6	141.7	117.3	118.4	118.5	124.8	121.8	128.3	128.9	124.1	130.6	131.3	128.4	135.1
December	148.6	147.1	137.4	146.0	120.2	120.8	119.7	126.9	125.1	133.1	132.7	125.4	134.2	134.7	134.2	140.2
1970																
June	154.7	155.0	144.6	154.4	125.3	*	123.4	*	131.3	*	141.9	132.4	141.1	141.5	139.0	147.3

<sup>1</sup>June 1962=100.0

<sup>2</sup>December 1965=100.0

<sup>3</sup>U.S. figures are for "fractured neck of femur"; California figures are for "closed reduction of Colle's type fracture."

<sup>4</sup>December 1963=100.0

\* data not available

tionally, slightly faster than the 5.3 percent rate in California.

During the same period, the index for obstetrical care also showed a faster increase nationally than in California—5.1 against 3.6 percent. In contrast, fees for herniorrhaphy rose faster in California (6.9 percent) than they did in the total U.S. (5.6 percent). Fees for tonsillectomy and adenoidectomy showed almost identical increases in California and the U.S. during this six-month period (5.0 percent and 5.1 percent, respectively). No recent U.S. data are available for the three remaining procedures shown in the table.

The long-term trends shown in the table generally parallel the comparisons between California and the nation in the entire physician fee index, which was discussed in connection with Table 2. Among the eight procedures, individual indices of fees are significantly higher nationally in four cases, approximately equal in three, and higher in California in one case. These figures are of interest not only in themselves, but also because they tend to bear out the validity of the comparisons made between the two over-all indices of physicians' fees.

*Long-Term Trends Show Limited Geographic Variations*

Fees for home visits have shown almost the same rate of increase nationally as in California since 1962. During this period, the average charge for a home visit increased 54.7 percent in California and 55.0 percent in the U.S. It is interesting to note that the 54.7 percent change for home visits in California is considerably higher than the 44.7 percent increase in office visits for the state during the same period. In contrast, home and office visits, nationally, have increased at almost exactly the same rate (55.0 percent and 54.4 percent, respectively).

Fees for office visits rose faster nationally than in California during the eight-year period shown in the table. The two indices were generally similar through mid-1966, after which time the national figure began rising at a considerably faster rate.

In the four-year period between December 1965 and December 1969, the indices for prostatectomy and fracture reduction rose faster nationally than in California. Physicians' fees for prostatectomy showed a national increase of 26.9 percent and a statewide increase of only 19.7 per-

cent; fees for fracture reduction increased 33.1 percent in the U.S. and only 25.1 percent in California. It is important to remember that these smaller increases do not indicate that fees are lower in California but rather that the rate of change is slower.

Fees for cholecystectomy and for tonsillectomy and adenoidectomy have shown almost identical increases in California and the U.S. Fees for cholecystectomy rose 20.8 percent nationally and 20.2 percent in California between December 1965 and December 1969. Fees for tonsillectomy and adenoidectomy increased 41.5 percent in the U.S. and 41.1 percent in the state between June 1962 and June 1970. Both indices show that fees generally rose faster in California than nationally through June 1967 and that the pattern has been reversed since then. Cholecystectomy fees increased 14.0 percent in the U.S. and 10.3 percent in California between that time and December 1969; tonsillectomy and adenoidectomy fees increased 19.9 percent in the U.S. and 15.8 percent in California through June 1970.

This trend of fees rising faster nationally than in the state since 1967 is also illustrated in the index for obstetrical care. Until June 1967, the California index for that procedure consistently showed faster increases than the national index. Between June 1967 and June 1970, however, fees increased 23.0 percent nationally and a considerably slower 17.4 percent in California. In contrast, fees for herniorrhaphy increased consistently faster in California (41.9 percent) than nationally (32.4 percent) since that index was started in 1963.

**APPENDIX**

The following is a total list of 1964 California Medical Association **Relative Value Studies** procedures for which fee data are currently being collected.

RVS Code	Procedures
0175	Excision (including simple closure) of BENIGN cicatricial, fibrous, inflammatory, congenital, cystic, etc., lesion of skin, subcutaneous tissue or mucous membrane; one, lesion diameter up to ¼ inch
0444	Excision of cyst, fibro-adenoma or other benign tumor, aberrant breast tissue, duct lesion (including gynecomastia) or nipple lesion (including any other partial mastectomy) male or female, unilateral
0807	Fracture, distal end of radius (e.g. Colle's type), simple, closed reduction and casting
2111	Bronchoscopy, diagnostic



2992	Tonsillectomy, with or without adenoidectomy, under age 18 years	7100	Chest, single view (X-ray, diagnostic)
3261	Appendectomy	7101	Chest, two views (X-ray, diagnostic)
3380	Hemorrhoidectomy, internal and external	7307	Ankle, two views (X-ray, diagnostic)
3515	Cholecystectomy	7356	Upper gastro-intestinal tract, with or without delayed films
3631	Herniorrhaphy, Hernioplasty or Herniotomy; Inguinal, unilateral	8628	Complete blood count
3930	Cystoscopy, diagnostic, office, initial	8936	Complete routine urinalysis (chemical and microscopic)
4122	Circumcision, clamp procedure, new born	9004	Follow-up office visit, routine
4321	Transurethral resection of prostate, including control of post-operative bleeding, complete	9014	Follow-up home visit, routine
4614	Total hysterectomy (corpus and cervix) with or without tubes, and/or ovaries, one or both	9024	Follow-up hospital visit, routine
4821	Total obstetrical care including ante-partum care, obstetrical delivery, and post-partum care, (with or without low forceps, and/or episiotomy)	9028	Consultation requiring <b>Limited</b> examination and/or evaluation of a given system but not requiring a complete diagnostic history and examination, home, office or hospital
5400	Eye examination to include refraction, ophthalmoscopy, tonometry, gross visual field and muscle balance examination	9030	Consultation requiring <b>Complete</b> diagnostic history and examination and/or evaluation, office, home or hospital
		9101	Electrocardiogram with interpretation and report

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# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Induced Vivax Malaria Among Users of Intravenous Heroin

IN RECENT YEARS, malaria in California has been limited mainly to importation of disease by servicemen returning from overseas and foreign travelers. The parasites have been largely confined to such persons, spilling into the community only occasionally through blood transfusions. An isolated mosquito-borne outbreak in 1952-53 among 35 Campfire girls was traced to a serviceman who had acquired his infection in Korea. Within the past several months, however, a new pattern of malaria transmission has emerged in two southern California counties among parenteral narcotics users. The purpose of this brief report is to highlight the epidemiologic and public health implications of these outbreaks.

### Ventura Outbreak

The first outbreak was recognized in December 1970 when the Ventura County Health Department notified the State Health Department that four cases of malaria had been diagnosed in heroin using residents in a small Ventura County

town during the previous four weeks. Subsequent investigations revealed two more related cases. Of the six affected persons, all were male and four were non-veterans who had not been to an endemic malaria area or had blood transfusions. Common to all were a blood smear diagnosis of *Plasmodium vivax*, and a history of shared heroin and intravenous injection equipment. The two Vietnam veterans had a history of malaria while on active duty, one sixteen months and the other five months previously. The veteran who had had malaria five months previously had not sought medical attention, but was found to have *P. vivax* on a thin blood smear examination during the course of the epidemiologic investigation. He admitted to intermittent fevers and chills over the previous several months for which, following return to the United States, he sporadically took quinine and Dapsone pills, the remainder of anti-malarial medication left over from Vietnam. This veteran was named as a contact by all of the other patients.

### Bakersfield Outbreak

In late February 1971, the State Health Department was notified of five cases of *P. vivax* malaria among male non-veterans which were associated with parenteral narcotics use in the Bakersfield (Kern County) area. Preliminary information indicated that these cases had no known association with the December cluster of induced vivax cases in Ventura County. Review of the Bakersfield cases indicated the probability of an extensive outbreak and an intensive epidemiologic investigation was promptly begun.



A malaria clinic was established in Bakersfield through the combined efforts of the Kern County Health Department, local medical organizations, the Center for Disease Control, Atlanta, Georgia, and the State Health Department. The malaria clinic was established to interview persons suspected of having the disease and all contacts, to obtain thick and thin peripheral blood smears and sera, and to administer presumptive treatment.

Through clinic activities approximately 450 heroin-using contacts were identified, and more than 325 of them received presumptive or "epidemiologic" treatment. Treatment of induced vivax malaria consists of chloroquine tablets, 1.0 gram followed by 0.5 gram six hours later and then 0.5 gram per day for the next two days, for a total dosage of 2.5 grams. Primaquine is not necessary since there is no exo-erythrocytic (tissue) phase with induced *P. vivax* infection. Only mosquito transmitted *P. vivax* infection has an exo-erythrocytic stage. All persons in the Bakersfield area who had been sharing parenteral narcotics were considered potentially exposed and epidemiologic treatment of all who had been exposed was given, as in the model of gonorrhea. Primaquine treatment in addition to chloroquine was given only to those persons with a history of military service in Southeast Asia.

The investigation found a total of 45 blood smear-confirmed cases of *P. vivax* infection plus an additional seven probable cases in which blood smear was negative but the indirect fluorescent antibody test was positive for malaria. The latter seven all had a history of sharing heroin with smear-positive patients. It was mainly young males who were affected; there were only five females and three patients over 30 years of age in the group. All were Caucasian, the majority Mexican-American. The majority of patients used heroin daily and all shared heroin and injection equipment with one or more other patients, the average being eight. Patients became ill between November 1970 and the end of March 1971. Only one became ill after the first week of March, when the clinic was established. As in Ventura County a Vietnam veteran was the apparent source of infection. No link could be established between the Ventura and Bakersfield cases. Only one instance of transmission beyond Bakersfield has been recognized. A Sutter County resident who acquired malaria in Bakersfield subsequently infected a

fellow heroin user after his return to Sutter County.

## Malaria and Narcotics Use

From 300 to 500 cases of malaria among Vietnam returnees are reported annually in California. Undoubtedly, more cases occur which are either not diagnosed or not reported. The documented, increasing use of heroin by troops in Vietnam and the United States coupled with the occurrence of malaria in this group most likely will give rise to more outbreaks of this type. Malaria can thus be added, along with hepatitis, as another medical symptom of the drug abuse problem in California.

Of the 374 cases of malaria reported in California in 1970 in which a species diagnosis was stated, 82 percent were *P. vivax* and 13 percent were *P. falciparum*; *P. malariae*, *P. ovale* and mixed infections accounted for the remaining 5 percent. Although *P. vivax* is the predominant species found in California, *P. falciparum* with its associated high mortality in non-immune populations would pose a serious danger if it were introduced. During the 1930's induced falciparum malaria in New York City heroin addicts was common. In various studies the mortality rate in this group ranged from 16 to 80 percent. It also was noted that these patients had symptoms not always typical of malaria. The majority of non-comatose patients complained of chills, tremulousness, vague aches and pains, cough, headache and feverishness. Most patients attributed these complaints to drug withdrawal or adulterated drugs. It should be kept in mind that heroin users with "withdrawal symptoms" may be in the early stages of cerebral malaria.

## Public Health Significance

At the time of these two outbreaks there were virtually no *Anopheles* mosquitoes in these areas, and thus the potential for mosquito-transmitted disease was remote. To the best of our knowledge, this is true the year around. However, there are *Anopheles* mosquitoes in large numbers starting at about the mid-San Joaquin Valley and going north to the northern tip of the Sacramento Valley, and also on the Western edge of the Sierra foothills. In this area, therefore, mosquito transmission of malaria can occur. The considerable effort expended in finding cases and treating as many contacts as possible in Bakersfield may have

been sufficient to control the outbreak. However, since many potentially exposed contacts could not be located for epidemiologic treatment, needle-associated malaria may continue in this population group. Also, as with gonorrhea, it is conceivable that a "ping pong" effect may occur if treated contacts continue to share needles with persons having undetected and untreated malaria since there is little acquired immunity to induced malaria, especially if treated promptly. The mobility of this population and their expanding social circles can promote spread of malaria infection to other locales, such as occurred in Sutter County.

The diagnosis of malaria should be considered in all intravenous drug users with fever and chills. Thick and thin blood smears should be examined on all suspected cases and positive smears for-

warded via local health departments to the State Microbial Diseases Laboratory for confirmation. Malaria cases should be reported promptly to local health departments so that necessary investigation can be begun without delay. Presumptive treatment of all needle-sharing contacts is recommended on an epidemiologic basis. Treatment varies according to the species of malarial parasite identified or suspected. Recommended treatment schedules are given in *Control of Communicable Diseases in Man*, 11th Edition, American Public Health Association, 1970.

Unless vigilance to detect possible cases of malaria in drug users is vigorously exercised, malaria may spread through shared needles and syringes and the risk of mosquito transmission may increase in receptive areas as summer approaches.

#### OCULAR SIGNS OF CAROTID ARTERY DISEASE

"Ophthalmologists have been extremely interested in the signs and symptoms of carotid artery disease and, in particular, the one component which may bring the patient to the eye doctor—the visual disturbance associated with intermittent amaurosis fugax or ipsilateral blindness. . . . Presumably if the carotid artery is partially stenosed, microemboli might leave an area of a plaque, rapidly dissipate through the retina, and lead to transient visual disturbance.

"According to a recent nationwide study by the National Institutes of Health, approximately 50 percent of patients with amaurosis fugax will suffer a major stroke within three years of the initial symptom and/or sign. It therefore behooves the ophthalmologist to utilize any available techniques except angiography to elicit findings indicative of carotid occlusive disease."

—MILES A. GALIN, M.D., New York City  
Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 17, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.



# In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

CLARK, ADRIAN E., Chula Vista. Died April 6, 1971 in National City of arteriosclerotic coronary thrombosis, aged 79. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1921. Licensed in California in 1921. Doctor Clark was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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\*

COHN, HOWARD J., Daly City. Died April 3, 1971 of heart disease, aged 38. Graduate of New York University College of Medicine, New York, 1958. Licensed in California in 1961. Doctor Cohn was a member of the San Mateo County Medical Society.

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DOYLE, JOHN BENEDICT SR., Los Angeles. Died March 27, 1971 in Los Angeles of heart disease, aged 76. Graduate of Rush Medical College, Chicago, 1917. Licensed in California in 1931. Doctor Doyle was a member of the Los Angeles County Medical Association.

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DUNN, JOHN SIEVER, Santa Rosa. Died April 24, 1971 at Sea Ranch of heart disease, aged 45. Graduate of University of Oklahoma School of Medicine, Oklahoma City, 1949. Licensed in California in 1954. Doctor Dunn was a member of the Sonoma County Medical Society.

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\*

EDWARDES, ARTHUR FRANCIS, Los Angeles. Died April 4, 1971 in Happy Valley of massive coronary occlusion, aged 54. Graduate of University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Edwardes was a member of the Los Angeles County Medical Association.

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\*

HOMBACH, FRANCIS J., Santa Barbara. Died December 14, 1970, aged 76. Graduate of Creighton University School of Medicine, Omaha, 1916. Licensed in California

in 1927. Doctor Hombach was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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HORNER, CLYDE DALE, San Francisco. Died March 15, 1971 of coronary artery disease, aged 76. Graduate of University of Oregon Medical School, Portland, 1924. Licensed in California in 1925. Doctor Horner was a member of the San Francisco Medical Society.

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NICHOLS, DONALD JAY, South San Francisco. Died April 3, 1971 in Palo Alto, aged 45. Graduate of University of Michigan Medical School, Ann Arbor, 1956. Licensed in California in 1958. Doctor Nichols was a member of the San Francisco Medical Society.

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NIELSEN, HAROLD W., Fowler. Died March 18, 1971 in Fowler, aged 77. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1916. Licensed in California in 1916. Doctor Nielsen was a member of the Fresno County Medical Society.

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NUZUM, FRANKLIN R., Santa Barbara. Died March 19, 1971, aged 83. Graduate of Rush Medical College, Chicago, 1913. Licensed in California in 1922. Doctor Nuzum was a member of the Santa Barbara County Medical Society.

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\*

ODLE, VAN A., Bullhead City, Arizona. Died March 3, 1971 in Bullhead City of heart disease, aged 60. Graduate of University of Tennessee College of Medicine, Memphis, 1934. Licensed in California in 1951. Doctor Odle was a member of the San Bernardino County Medical Society.

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\*

PAIGE, GEORGE ALEXANDER, Anaheim. Died March 16, 1971 in Anaheim, aged 95. Graduate of University Medical College of Kansas City, Missouri, 1907. Licensed in California in 1922. Doctor Paige was a member of the Orange County Medical Association.

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\*

PALMER, FRIEDA MEYERFELD, San Carlos. Died March 16, 1971 in San Carlos, aged 63. Graduate of Universität Heidelberg Medizinische Fakultät, Jena, Thuringia, Germany, 1933. Licensed in California in 1935. Doctor Palmer

was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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\*

POLMETEER, FRANK EDWARD, Long Beach. Died March 29, 1971 in Santa Monica of metastatic adenocarcinoma, aged 62. Graduate of State University of Iowa College of Medicine, Iowa City, 1936. Licensed in California in 1946. Doctor Polmeteer was a member of the Los Angeles County Medical Association.

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SIPPI, THEODORE MISCHER, Santa Monica. Died April 14, 1971 in Santa Monica, aged 48. Graduate of New York University College of Medicine, 1948. Licensed in California in 1953. Doctor Sippi was a member of the Los Angeles County Medical Association.

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\*

STEGEMAN, DIRK EDMUND, North Hollywood. Died April 9, 1971 of coronary artery disease, aged 74. Graduate of University of Cincinnati College of Medicine, 1927. Licensed in California in 1927. Doctor Stegeman was a member of the Los Angeles County Medical Association.

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STIFFLER, CHARLES HOWLAND, Santa Rosa. Died November 2, 1970 in Santa Rosa, aged 47. Graduate of Northwestern University Medical School, Chicago, 1948. Licensed in California in 1951. Doctor Stiffler was a member of the Sonoma County Medical Society.

SZABO, ELEMER B., Los Angeles. Died April 14, 1971 in Baldwin Hills of myocardial infarction, aged 71. Graduate of Magyar Királyi Pázmány Péter Tudományegyetem Orvosi Fakultása, Budapest, 1923. Licensed in California in 1953. Doctor Szabo was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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\*

TREUSCH, JEROME VICTOR, Beverly Hills. Died March 22, 1971 in Beverly Hills of coronary artery disease, aged 56. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in California in 1944. Doctor Treusch was a member of the Los Angeles County Medical Association.

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\*

VOLSTORFF, CLIFTON H., San Jose. Died December 5, 1970 near Los Banos of coronary artery occlusion, aged 55. Graduate of the University of Oregon Medical School, Portland, 1951. Licensed in California in 1952. Doctor Volstorff was a member of the Santa Clara County Medical Society.

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\*

ZIMMERMAN, NORVAL FRANKLIN, Los Angeles. Died April 18, 1971 in San Clemente of heart disease, aged 50. Graduate of Northwestern University Medical School, Chicago, 1946. Licensed in California in 1948. Doctor Zimmerman was a member of the Los Angeles County Medical Association.

## MARK IT!

101st Annual Scientific Assembly

California Medical Association

February 12-16, 1972

San Francisco Hilton Hotel

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**Description:** Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorimetrically active components, sodium levothyroxine ( $T_4$ ) and sodium liothyronine ( $T_3$ ). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

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**Warnings:** Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid, and dosage should be started at a very low level and increased gradually.

**Precaution:** As with all thyroid preparations this drug will alter results of thyroid function tests.

**Adverse Reactions:** Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

**Dosage and Administration:** Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR,  $T_3$   $^{131}$ I resin sponge uptake,  $T_3$   $^{131}$ I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of  $T_4$  and  $T_3$  is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

**Instructions for Use:** The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid,  $T_4$  (sodium levothyroxine),  $T_3$  (sodium liothyronine), or  $T_4/T_3$  (liotrix).

Dose of Proloid (thyroglobulin)	Dose of desiccated thyroid	Dose of $T_4$ (sodium levothyroxine)	Dose of $T_3$ (sodium liothyronine)	Dose of liotrix ( $T_4/T_3$ )
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.

**Overdosage Symptoms:** Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

**How Supplied:**  $\frac{1}{4}$  grain;  $\frac{1}{2}$  grain; scored 1 grain;  $1\frac{1}{2}$  grain; 3 grain; and scored 5 grain tablets, in bottles of 100 & 1000; and scored 2 grain tablets in bottles of 100.

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### MEETINGS

**101ST ANNUAL SCIENTIFIC ASSEMBLY** of the California Medical Association, February 12-16, 1972. San Francisco Hilton Hotel, Mason and O'Farrell Streets, San Francisco.

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**GUEST SPEAKER:** Bernard L. Segal, M.D. Associate Professor of Medicine Hahnemann Medical Col. and Hospital Philadelphia, Pennsylvania

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# BOOKS RECEIVED

*Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

**ALZHEIMER'S DISEASE AND RELATED CONDITIONS**—A Ciba Foundation Symposium—Edited by G.E.W. Wolstenholme and Maeve O'Connor, J. & A. Churchill, 104 Gloucester Place, London, 1970. 316 pages, no price listed.

**ATLAS OF BONE-MARROW PATHOLOGY**—Four Edition—M.C.G. Isaacs, M.D., M.Sc., F.R.C.P., Professor of Clinical Haematology, University of Manchester; Physician to the United Manchester Hospitals. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1971. 83 pages, \$9.50.

**BASIC BIOCHEMISTRY**—Third Edition—Max E. Rafelson, Jr., Ph.D., Associate Dean, Biological and Behavioral Sciences and Services, and Professor of Biochemistry, Rush Medical College, Rush-Presbyterian-St. Luke's Medical Center, Chicago; Stephen B. Binkley, Ph.D., Dean, Graduate College, and Professor, Biological Chemistry, University of Illinois Medical Center, Chicago; and James A. Hayashi, Ph.D., Professor Biochemistry, Rush Medical College. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1971. 406 pages, \$7.95, paperback, and \$11.00, hardbound.

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**BETTER MEDICAL WRITING**—Charles Thorne, M.D. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017). 96 pages, \$5.00.

**CALORIES AND CARBOHYDRATES**—A Dictionary of 7500 Brand Names and Basic Foods with Their Caloric and Carbohydrate Count—Barbara Kraus; Foreword by Edward B. Greenspan, M.D. Grosset & Dunlap, Inc., 51 Madison Avenue, New York, N.Y. (10010), 1971. 322 pages, \$7.95.

**CARE OF THE NURSING-HOME PATIENT**—A Textbook for Nurse's Aides, Nursing Assistants, Orderlies, and Attendants—Edited by Philip W. Brickner, M.D., Medical Director, Village Nursing Home, New York City; Chief of Ambulatory Services and Attending Physician, Department of Medicine, St. Vincent's Hospital and Medical Center of New York. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1971. 342 pages, \$6.95.

**CELLULAR ASPECTS OF NEURAL GROWTH AND DIFFERENTIATION**—UCLA Forum in Medical Sciences—Number 14—Proceedings of a conference held November, 1969; Sponsored by the School of Medicine and the Brain Research Institute, University of California, Los Angeles—Edited by Daniel C. Pease, Chairman and Editor, Department of Anatomy, University of California Press, 2223 Fulton Street, Berkeley, Ca. (94720), 1971. 520 pages, \$25.00

**CEREBRAL VASCULAR DISEASES**—Transactions of the Seventh Conference Held under the Auspices of American Neurological Association and American Heart Association, Council on Cerebrovascular Disease, Princeton, N.J.; January 7-10, 1970—James F. Toole, Chairman; John Moosy and Richard Janeway, Editors. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1971. 258 pages, \$9.75.

**CLINICAL UROGRAPHY**—An Atlas and Textbook of Roentgenologic Diagnosis—Volumes 1-3—Third Edition—John L. Emmett, M.D., M.S. (Urology), Emeritus Consultant, Section of Urology, Mayo Clinic; Emeritus Professor of Urology, Mayo Graduate School of Medicine (University of Minnesota), Rochester; and David M. Witten, M.D., M.S. (Radiology), Formerly Consultant, Section of Diagnostic Roentgenology, Mayo Clinic; Assistant Professor of Radiology, Mayo Graduate School of Medicine. W.B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 2101 pages, \$84.00.

**EXERCISES IN DIAGNOSTIC RADIOLOGY**—Volume Two—The Abdomen—Lucy Frank Squire, M.D., Lecturer on Radiology, Harvard Medical School; Visiting Radiologist, Massachusetts General Hospital, Boston; William M. Colaiace, M.D., Lecturer in Medical Science, Brown University; Radiologist, Roger Williams Hospital, Providence; and Natalie Strutynsky, M.D., Assistant Professor, Radiology, New York Medical College, New York City. W.B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 88 pages, \$4.95.

**KIDNEY DISEASE IN THE YOUNG**—Elvira Goettsch, M.D., Associate Attending Pediatrician to Babies Hospital, Columbia-Presbyterian Medical Center, New York City; Associate Professor of Pediatrics, University of Southern California School of Medicine; Assistant Medical Director, Childrens Hospital, Los Angeles; Based on Studies Carried out in Collaboration with the Late John D. Lytle, M.D. W.B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 305 pages, \$22.50.

**LEPROSY IN FIVE YOUNG MEN**—George J. Hill, II, M.D., Assistant Professor of Surgery, University of Colorado School of Medicine, Denver; formerly Clinical Associate, National Institutes of Health, Bethesda, Maryland. Colorado Associated University Press, 1424 15th Street, University of Colorado, Boulder, Colorado (80302), 1971. 204 pages, \$8.00.

**THE LOW FAT, LOW CHOLESTEROL DIET**—Revised Edition—Clara-Beth Young Bond, R.D., Consulting Dietitian, Sacramento; E. Virginia Dobbins, R.D., Former Senior Dietitian, E.V. Cowell Memorial Hospital, University of California, Berkeley; Helen F. Gofman, M.D., San Francisco; Helen C. Jones, Home Economist, Berkeley; and Lenore Lyon, Homemaker, San Jose, California. Doubleday & Company, Inc., Garden City, New York, 1971. 512 pages, \$7.95.

**A MANUAL OF DERMATOLOGY**—Donald M. Pillsbury, M.A., M.D., Professor and former Chairman, Department of Dermatology, School of Medicine, University of Pennsylvania; Colonel M.C. AUS (ret). W.B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 299 pages, with 263 figures in color, \$15.00.

**MEDICAL JURISPRUDENCE**—John R. Waltz, LL.B., Professor of Law, Northwestern University School of Law, and Lecturer in Medical Jurisprudence, Northwestern University Medical School, Chicago; and Fred E. Inbau, LL.B., LL.M., Professor of Law, Northwestern University School of Law. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1971. 398 pages, \$10.95.

**MEDICAL RESIDENTS' MANUAL**—Third Edition—William J. Grace, M.D., Director, Department of Medicine, St. Vincent's Hospital and Medical Center of New York; Professor of Clinical Medicine, New York University School of Medicine; Richard J. Kennedy, M.D., Associate Director of Medicine, St. Vincent's Hospital and Medical Center; Clinical Professor of Medicine, New York University School of Medicine; and Frank B. Flood, M.D., Chief Cardiologist, St. Joseph's Hospital, Yonkers; Attending Physician, Yonkers General Hospital. Appleton-Century-Crofts, Educational Division/Meredith Corporation, 440 Park Avenue South, New York, N.Y. (10016), 1971. 439 pages, \$6.75.

**MOLECULAR PROPERTIES OF DRUG RECEPTORS**—A Ciba Foundation Symposium—Edited by Ruth Porter and Maeve O'Connor, J. & A. Churchill, 104 Gloucester Place, London, 1970. 298 pages, no price listed.

**PSYCHOLOGY OF EMOTION**—Self Discipline by Conscious Emotional Containment—John M. Dorsey, M.D. Published by Center for Health Education, 4421 Woodward Avenue, Detroit, Michigan (48201), 1971. 174 pages, \$6.95.

**PSYCHOSOMATIC MEDICINE**—Current Journal Articles—A Collection of Current Articles Related to Psychosomatic Medicine—Compiled by J. Elizabeth Jeffress, M.D., Assistant Clinical Professor, Department of Psychiatry and Department of Ambulatory Community Medicine, University of California School of Medicine, San Francisco; Assistant Clinical Professor, Department of Psychiatry, Stanford University; Chief of Professional Education, Agnews State Hospital, San Jose. Medical Examination Publishing Company, Inc., 65-36 Fresh Meadow Lane, Flushing, New York (11365), 1971. 380 pages, \$12.00.

**SENSORINEURAL HEARING LOSS**—A Ciba Foundation Symposium—Edited by G.E.W. Wolstenholme and Julie Knight, J. & A. Churchill, 104 Gloucester Place, London, 1970. 358 pages, no price listed.

**TASTE AND SMELL IN VERTEBRATES**—A Ciba Foundation Symposium—Edited by G.E.W. Wolstenholme, and Julie Knight, J. & A. Churchill, 104 Gloucester Place, London, 1970. 402 pages, no price listed.

















